ANTIBIOTIC RESISTANCE

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT

OF THE

COMMITTEE ON
SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES

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ANTIBIOTIC RESISTANCE

TUESDAY, DECEMBER 18, 1984

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT,
Washington, DC.

The subcommittee met, pursuant to call, at 9:30 a.m., in room 2325, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Mr. GORE. The subcommittee will come to order. I'd like to welcome our witnesses and guests.

Today we begin a 2-day consideration of an important public health subject, that of antibiotics and antibiotic resistance. Antibiotics are, of course, truly wonder drugs and have saved millions of lives since their discovery some 40 years ago. In 1900, the life expectancy of an American at birth was only about 47 years, while by 1950, life expectancy had increased to 68 years.

A big part of the reason for this dramatic change was the introduction of antibiotics for treatment of disease. In 1900, infectious diseases, particularly pneumonia and tuberculosis, were the leading causes of death. This is no longer true today, at least not in the developed countries where most individuals have access to these modern miracle drugs.

In 1983, over 195 million prescriptions were written for antibiotics for human patients in the United States. This accounts for about 13 percent of all U.S. drug prescriptions for that year.

Unfortunately, however, in some ways, bacteria are as ingenious as we are and have acquired the ability to render antibiotics ineffective and to disarm some of our best medical weapons.

Bacteria accomplish the inactivation of antibiotics with antibiotic resistance genes. Once resistance genes are acquired by bacteria, infections become much more difficult to treat. In fact, antibiotic resistance can result in life-threatening situations and even fatalities. Elderly people and young infants seem to be the most vulnerable to severe illness and death from resistant infections. The extent to which antibiotic resistance becomes widespread is thus a critical public health issue.

Over the next 2 days, we will examine the development of antibiotic resistance, what causes it, what its impacts are and what can be done about it. Today we will focus on the question of whether or not the subtherapeutic use of antibiotics to promote growth in livestock represents a health hazard to humans.

Tomorrow we will take up the consideration of how antibiotics are used and misused in human medicine. Together, these two sub-

jects cover the predominant uses of antibiotics and we will try to determine which, if either, represents the greater threat to human health, or whether they are both equally troubling.

Subtherapeutic doses of antibiotics—that is, doses lower than those needed to treat actual disease—have been added to animal feeds since the 1950's. Around that time, it was discovered that such additives were associated with improvements in the efficiency with which animals convert feed to meat.

In promoting growth, antibiotics apparently allow farmers to use less feed to produce more meat, which is clearly good for the meat industry and for consumers. Some producers maintain, in fact, that this is an essential part of the economics of meat production.

On the other hand, some critics say that evidence is mounting that resistant bacteria are developing in food animals, causing serious illness in human beings, and are compromising the use of important drugs in human medicine. The accusation that antibiotics used in animal feed represent a health hazard to people has been controversial for quite a long time.

In 1977, the FDA proposed to ban penicillin from growth-promotion use and to place restrictions on the use of tetracycline in animal feeds. These two drugs, penicillin and tetracycline, are the most important human drugs routinely fed to livestock.

In 1977, however, FDA did not succeed in convincing Congress that the postulated health hazard is real. Instead, Congress requested that more scientific information be collected. When the National Academy of Sciences Committee looked at the question in 1980, it concluded that the health hazard could not be proven or disproven with the information that existed at the time.

Recently, however, a great deal of new scientific data has come to light. Researchers at the Centers for Disease Control have published two new studies and an additional project by the Seattle-King County Health Department for FDA has also been recently completed.

Today we will look into this new evidence to try to determine whether the scientific information is really more conclusive now than it was earlier.

Without objection, I would like to include in the record at this point any statement that the minority, ranking minority member, Mr. Skeen, wishes to include.

I want to welcome a panel of experts to discuss the strengths and weaknesses of the latest scientific information on the livestock feed issue.

Our first panel will consist of Dr. Mitchell Cohen, with the Centers for Disease Control in Atlanta; Dr. Thomas O'Brien, from the Department of Medicine at Brigham and Women's Hospital in Boston; Dr. Virgil Hays, with the Department of Animal Sciences at the University of Kentucky in Lexington; and Dr. Leon Sabath, professor of medicine at the University of Minnesota in Minneapolis.

I'd like to welcome all four of you and express the subcommittee's gratitude for your willingness to help us in this effort. Our procedure is that we take testimony from all members of a panel before having questions for that panel, so we'll proceed on that basis.

Without objection, the entire prepared written statements you have will be included in full in the record. If you wish to summarize any portion of them, feel free to do so, because the entire statement will—will appear in the record.

We'll begin now with Dr. Mitchell Cohen from the CDC and, again, welcome, and please proceed, Dr. Cohen.

[The biographical sketch of Dr. Cohen follows:]

December, 1984

CURRICULUM VITAE

Mitchell Lewis Cohen, M.D.

Date of Birth:	May 17, 1948	
Place of Birth:	Washington, D.C.	
Social Status:	Married:	Jean
	Children:	one daughter, Lindsay, Born 1977 one son, David, Born 1982
Education:	1970	A.B., Duke University, Durham North Carolina
	1973	M.D., Duke University
	1973-74	Medical Intern, Parkland Memorial Hospital-Veterans Administration Hospital Dallas, Texas
	1974-76	Medical Resident, Parkland Memorial Hospital-Veterans Administration Hospital
	1975-76	Chief Medical Resident, Parkland Memorial Hospital-Veterans Administration Hospital
Professional Experience:	1976-78	Epidemic Intelligence Service Officer Enteric Diseases Branch, Bacterial Diseases Division, Bureau of Epidemiology Center for Disease Control
	1978-79	Chief, Antimicrobial Drug Resistance Activity, Hospital Infections Branch, Bacterial Diseases Division, Bureau of Epidemiology, Center for Disease Control
	1979-81	Infectious Diseases Fellowship University of Washington, Seattle, Washington, CDC Career Development Program
	1981-82	Chief, Molecular Epidemiology Activity Enteric Diseases Branch Division of Bacterial Diseases Center for Infectious Diseases Centers for Disease Control

1982-84	Assistant Chief, Enteric Diseases Branch Division of Bacterial Diseases Center for Infectious Diseases Centers for Disease Control
1984-	Assistant Director for Medical Science Division of Bacterial Diseases Center for Infectious Diseases Centers for Disease Control

Certification:

Diplomate, American Board of Internal Medicine, 1976; Subspeciality in Infectious Diseases, 1982

Medical licensure, Texas, 1975-1982
Virginia, 1975-77, Washington 1979-present

Honors:

Phi Beta Kappa, Duke University, 1969

Merck Award, Duke University, 1970

Magna cum Laude graduate, Duke University, 1970

Medical Societies:

American Medical Association, 1974 - 1980

American College of Physicians - Associate, 1975-1977, Member, 1977 to present

American College of Physicians - Fellow, 1984

Publications:

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18. Riley LW and Cohen ML: Letter--Plasmid Profiles and Salmonella epidemiology. Lancet, March 6, 1982, p573.

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1. Transmission of antibiotic resistance from animals to man. Epidemic Intelligence Service Conference, Atlanta, May 1977.

2. Epidemiology of acid fast water bacteria in the United States. American Society for Microbiology, Las Vegas, May 1978.

3. Nosocomial Legionnaires' Disease: A Common Source Outbreak. International Symposium on Legionnaires' Disease, November 1978.

4. Legionnaires' Disease as a cause of fatal nosocomial pneumonia. International Symposium on Legionnaires' Disease, November 1978.

5. Common R-plasmid in Staphylococcus aureus and epidemidis during a nosocomial outbreak. 20th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 1980.

6. Bacteremia after marrow transplant: relationship to bacterial colonization and usefulness of surveillance cultures. 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 1980.

7. Antigenic characteristics of Enterobacteriaceae associated with Reiter's syndrome. International Conference on the Spondyloarthropathies, Dallas, Texas, May 30-June 2, 1984.

STATEMENTS OF DR. MITCHELL COHEN, CENTERS FOR DISEASE CONTROL, ATLANTA, GA; DR. THOMAS O'BRIEN, DEPARTMENT OF MEDICINE, BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MA; VIRGIL W. HAYS, DEPARTMENT OF ANIMAL SCIENCES, UNIVERSITY OF KENTUCKY; AND DR. LEON SABATH, PROFESSOR OF MEDICINE, UNIVERSITY OF MINNESOTA, MINNEAPOLIS, MN

Dr. COHEN. Thank you.

Mr. Chairman, I am Mitchell Cohen, Assistant Director for Medical Science, Division of Bacterial Diseases, Center for Infectious Diseases, Centers for Disease Control, U.S. Public Health Service.

I'm pleased to respond to the subcommittee's invitation to discuss our investigation of an interstate outbreak of multiresistant Salmonella newport infections. Before I discuss the actual investigation and its implications, I'd like to provide some brief background information concerning the epidemiology of salmonellosis.

The Division of Bacterial Diseases is responsible for surveillance programs, reference activities, epidemic investigations and field and laboratory studies of bacterial diseases. Salmonellosis is one of the bacterial diseases for which the division is responsible. Salmonellosis is usually a diarrheal illness; however, Salmonella infections can extend to the blood and other organs, especially in infants, the elderly, and persons with compromised host defenses. Such infections may result in death.

Antibiotic treatment is not indicated in uncomplicated gastrointestinal infections, but when complications occur, antimicrobial therapy is required and can be life saving. The Centers for Disease Control has conducted surveillance of human salmonellosis in the United States since the early 1960's. Over 40,000 Salmonella infections are reported to the CDC by State laboratories each year and we estimate that as many as 4 million Salmonella infections may occur in the United States annually.

There are approximately 2,000 different serotypes of Salmonella, although 10 serotypes account for over 70 percent of Salmonella

isolated in the United States. Since most Salmonella isolates are common serotypes, scientists have attempted to identify subgroups by techniques such as phage typing and plasmid profile analysis. Using combined epidemiologic and laboratory techniques has given us a better understanding of where Salmonella come from and how they are spread.

In the United States, salmonellosis is transmitted primarily by foods of animal origin. Although Salmonella infections can be transmitted sometimes from human to human or from human to food to human, animal reservoirs have been repeatedly demonstrated to be the original source of the infecting organism. For example, such transmission may be the infant who acquires salmonellosis from its mother who had been infected by eating contaminated meat.

Recent studies show that a quarter to a third of Salmonella are resistant to multiple antimicrobials. When this resistance involves commonly used agents such as ampicillin and chloramphenicol, it jeopardizes the patient's treatment. There are instances when resistance has compromised therapy and resulted in the death of infected patients.

With this background, let us turn to the interstate Salmonella newport outbreak. In early 1983, laboratory-based surveillance of Salmonella infections by the Minnesota Department of Health showed a marked increase in isolates of Salmonella newport, an unusual serotype in that State. Many of the patients that were contacted by the State health department had been taking antibiotics for nondiarrheal illnesses just before the onset of their salmonellosis. Concerned that this outbreak was caused by a contaminated antimicrobial, the Minnesota Health Department and the Centers for Disease Control began a collaborative investigation.

Early in the investigation, contaminated antimicrobials were ruled out since patients had taken different antimicrobials from different pharmacies and different manufacturers. After several weeks of investigation, the investigators had identified 10 patients infected with the Salmonella newport that was resistant to ampicillin, carbenicillin, and tetracycline. Of these 10 cases, 7 had taken either amoxicillin or penicillin in the week before the onset of illness for a variety of symptoms unrelated to the subsequent salmonellosis. In several instances, patients had taken these drugs either without the prescription of the physician or without the physician's supervision.

Typically, the symptoms of salmonellosis began within 48 hours after the patients took the antimicrobials and these symptoms included high fever, severe abdominal cramps, and blood in the stools. Six patients were hospitalized for an average of 8 days.

Epidemiologic investigation in Minnesota to find the source of the epidemic Salmonella newport revealed that the patients had eaten no unusual foods, but all had eaten ground beef in the week before illness. At this point, the Minnesota phase of the investigation was concluded.

Laboratory work at the CDC on the Salmonella newport demonstrated that the resistance to ampicillin, carbenicillin, and tetracycline was conferred by genes which were present on a single plasmid. To identify additional cases of infection with this Salmonella

newport, the investigators reviewed State and Federal laboratory records for the surrounding States and interviewed patients that were infected with Salmonella newport that were resistant to the same antimicrobials.

In addition, we obtained all available human and nonhuman isolates of Salmonella newport in the six-State area for 1982 and the first half of 1983 and all available nonhuman Salmonella newport from the U.S. Department of Agricultural Veterinary Services Laboratory in Ames, IA.

In the subsequent epidemiologic investigation in the six-State area, eight more cases of infection were identified, four in South Dakota. All four South Dakota patients had taken penicillin before the onset of salmonellosis.

In one of these cases, the infection was hospital-acquired and transmitted by a contaminated sigmoidoscope used on an earlier patient. This patient received many antimicrobials and died with fever and other symptoms of septicemia 20 days after the endoscopy. The epidemic Salmonella newport was isolated from blood, from sputum, and stool specimens of this patient before he died.

The three surviving South Dakota patients lived on two farms and were related by a marriage. The isolates of Salmonella newport from the 10 cases in Minnesota and the available isolate from the one case in South Dakota were identical. They had the same resistance patterns and the same single-resistance plasmid.

Review of the animal isolates in the six-State area identified identical characteristics in only one isolate—a Salmonella newport strain that was isolated from the tissues of a calf that had died in November of 1982 during an outbreak of diarrheal disease in dairy cows on the farm of one of the South Dakota patients.

The epidemiologic investigation of the South Dakota cases, excluding the hospital-acquired case, revealed that the patients had not eaten together or socialized with one another in the previous year and the only common exposure these patients had was a relative's feedlot beef farm. Each of these patients had eaten beef from the farm's beef herd in 1982 and 1983.

The investigation next examined this connection. According to the farmer, the beef cattle had been well and had been fed subtherapeutic amounts of chlortetracycline throughout 1982 for growth promotion and disease prevention, but they were not fed any concentrations of therapeutic antimicrobials.

All 105 herd—head from this herd had been slaughtered in Minnesota in January 1983. Fifty-nine carcasses had been sent to Minnesota for processing into boxed beef. On the day after these 59 carcasses had been cut and packed in boxes in Nebraska, 40,000 pounds of boxed beef, which could have included beef from both the suspect herd and other herds, were sent to a meat brokerage firm near Minneapolis-St. Paul. The boxes were traced through the meat broker's computerized records to six of the seven supermarkets named as the source of ground beef by the eight patients in the initial outbreak who lived in the Minneapolis-St. Paul area. Beef was also shipped to a meat brokerage firm that supplied supermarkets used by patients outside the Minneapolis-St. Paul area.

To determine if this unique plasmid profile of a single resistance plasmid was common in Salmonella newport isolated from animals,

91 nonhuman isolates were examined, 9 of these from the 6-State area in 1982, and the first half of 1983, and 82 isolates from throughout the continental United States from October 1981 to September 1982. The only isolate from the dairy herd—only the isolate from the dairy herd was identical to the isolates from patients in the outbreak groups.

Several important points emerge from this investigation. First, the investigation demonstrates how difficult it is to untangle the complex chain of transmission by which resistant organisms from animals infect man. The difficulty in documenting these events in sequence has been important in the controversy over the use of antimicrobials in animal feeds because lack of the kind of evidence shown in this study has been cited by proponents of antimicrobial feed additives as demonstration of their safety.

The complexity of the chain of transmission is emphasized from this outbreak by the fatal nosocomial case. It's unlikely that investigation of that isolated case would have been able to retrace the infection from the patient back to the sigmoidoscopy procedure, to the other patient, to an ultimate food source. In addition, two household contacts of outbreak patients became ill long after the outbreak had ended, suggesting that there was secondary spread from family members. The Salmonella transmitted by apparent person-to-person spread were ultimately of animal origin.

This data suggests that the controversy which is regarded the relative importance of person-to-person and animal-to-person transmission of resistant enteric bacteria is based on an artificial distinction. Recent studies corroborate our suggestion that sporadic cases of Salmonella infection continue to occur after the introduction of bacteria through contaminated meat products. The ultimate reservoir of those sensitive and resistant Salmonella is most frequently the animal population.

The epidemiologic and laboratory evidence in this outbreak did not identify the ultimate source of the resistance plasmid that was found in the epidemic strain of Salmonella newport. It's unlikely that the beef herd was the original source of this resistance plasmid. Analysis of Salmonella newport from animals and human beings in the United States in the year before the outbreaks revealed the same plasmid in association with additional plasmids in isolates from 10 animal populations in four States in 1981 and 1982 and one patient with infection acquired in Mexico or Texas in June 1982.

Thus, the beef herd was probably not the original source of the resistance plasmid, but the use of the subtherapeutic antimicrobials in the herd's feed throughout 1982 provided a selective pressure for the persistence of the antimicrobial-resistant organism by suppressing sensitive organisms and thus reducing the competition for the resistant Salmonella newport.

This investigation also demonstrated that antimicrobial-resistant Salmonella can complicate the antimicrobial therapy of other bacterial infections and, in addition, it may be a complication of inappropriate antimicrobial use in humans since, as I mentioned before, several patients were taking antimicrobials that were prescribed to other family members, or were taking previously prescribed antimicrobials for an illness that had not been seen by a physician.

In summary, this investigation showed that identical Salmonella newport was recovered from 18 persons in four midwestern States; that this Salmonella newport was genetically distinct from all but 1 of over 160 Salmonella newport strains isolated from humans and animals during an 18-month period preceding the cluster of human cases. The one animal isolate identical to the human outbreak strain was recovered from a dairy herd on a farm adjacent to a beef herd fed subtherapeutic antimicrobials. The timing and geographic distribution of the human infections coincided with the slaughter and distribution of the beef herd.

Patients with Salmonella newport infections had either received their meat directly from the herd or had purchased it from supermarkets apparently supplied with meat from the herd.

Mr. Chairman, thank you for the opportunity to participate in this panel. I'll be happy to answer any questions you may have.

Mr. GORE. Well, thank you. That's a fascinating detective story and we'll hold off questions until the rest of the panel has completed their statements.

Dr. Thomas O'Brien, with the Department of Medicine at Brigham and Women's Hospital in Boston, we're delighted to have you here. Welcome. Please proceed.

[The biographical sketch of Dr. O'Brien follows:]

O'Brien, Thomas F. B'29, A.B. Holy Cross '50, M.D. Harvard '54. Physician and Director, Microbiology Laboratory, Brigham and Women's Hospital, Boston, MA 02115, Associate Professor, Medicine, Harvard Medical School, Chairman, WHO consultation group on Surveillance Antibiotic Resistance '82, Chairman, Task Force on Antibiotic Resistance, NIH Conference on Use of Antibiotics Worldwide '83-'86.

Dr. O'BRIEN. Thank you, Mr. Chairman, ladies and gentlemen.

I'm Dr. Thomas O'Brien of the Brigham and Women's Hospital in the Harvard Medical School in Boston, MA.

I've been asked to comment on the technologies available to identify specific antibiotic resistance plasmids and particularly as background for the plasmids detected by Dr. Cohen and his coworkers.

May we see the first slide please. [Slide.]

Mr. GORE. In spite of the wall coverings in this room, we sometimes have a less than perfect mastery of technology here. [Laughter.]

Dr. O'BRIEN. Thank you—oh great, thank you. OK, I'll push for the first one. Yes. Oh, great. Is there a zoom? I guess those—if you can make it a bit larger with the zoom. Is there a zoom attachment on that? Well, possibly—we'll work with that.

This is just to show that the—this is an electron—I think to give us tangible to look at—an electron micrograph showing two copies of what is probably the same plasmid. You can see them as those loops and I'd like to remind you at this time that a plasmid is a sort of a miniature chromosome, maybe one-tenth to one-hundredth the size of the bacterial chromosome and each of them—either one of these copies, identical, we presume, identical copies—either one of these is made of a sequence of DNA bases, 4 different bases, and there may be 20,000, 30,000, 40,000 bases along this long extended chain of DNA bases, and, of course, the bases—a sequence of 1,000 or more bases will encode all the information to make a particular protein that is used by the cell and so there may be 30—on one of these plasmids maybe 30 or 40 genes for different proteins, the ge-

netic information for the different proteins and the plasmid will have some of these genes that are there to make up—to care for its own reproduction, to arrange for the mechanisms needed to get the plasmids transferred from one bacteria cell to another, which is the way they're spread, but some of the genes—perhaps 3, 4, 5, 6 of them will encode for antibiotic resistance genes, for proteins that will make the bacterial cell resistant to 1 or more—each to one or more of the various antibiotics.

And so these are the vehicles for the spread of antibiotic resistance between bacteria, or as in the case that Dr. Cohen described this morning, to be carried consistently within one bacterial strain and carry that strain to make that strain resistant wherever it's carried.

Another point I would like to focus on now is that for these epidemiological purposes, as with Dr. Cohen's study this morning, it's important to be able to tell one plasmid from another or to be able to say that two plasmids found in remote places are identical or at least closely related. And since they are, each one of them has to have a very specific sequence of DNA bases throughout this whole chain length. One way to do it, of course, would be to read chemically, to identify the whole sequence of bases.

That's technically possible—nearly possible now—but extremely laborious and time consuming and yet, by available techniques impractical probably for epidemiological purposes. So another technique is used and was used—we had used it and now Dr. Cohen has used it and his colleagues in his investigation, which accomplishes the same thing in a different way. The technique depends upon the existence of what are called restriction endonuclease enzymes.

A restriction endonuclease enzyme recognizes a certain specific sequence of six of these bases, goes along the chain, runs along that chain until it finds those six bases, cuts the chain in two at that point, and then will run along to the next place where those six bases occur and cut it in two again.

The analogy, I think, is for identifying plasmids in this way would be to take two texts, two books that you were given, and you might be asked whether this is the same novel or not. One way would be to read it all, to identify the sequence of words, which we said would be perhaps too difficult for the bases. The other technique possible would be to take one commonly occurring word—perhaps the word "there" I've used as an example—have your word processor read through the text until you come to the word "there," note that and go on until it occurs again maybe thousands of words later and then have the word processor count the number of letters and spaces in between those two occurrences, and if, when you get done running both of those texts through that same process, if the intervals were exactly the same, you would conclude that the possibility of they—of there being two different novels, possible, of course, but unthinkably small by chance could have the same sequence of intervals between these particular spots. So also, if you apply restriction endonuclease enzymes to a chain like this and cut it in 8 or 10 places, if the intervening fragments are the same on the two, then you would conclude that the chances of them being other than closely related are unthinkably small.

The next slide——

[Slide.]

Dr. O'BRIEN [continuing]. Shows the result of doing that. When you cut—after you have taken—you extract plasmids, pure plasmids, you extract the—as I say, you take the plasmid; you digest it, each one of them, each copy of the plasmid from wherever you got it, with these enzymes, you then put them in a gel through which they're moved by an electrical current and they sort themselves out by size. Their location vertically in these vertical lanes is exactly a measure of their size, exactly a function of their size. And so if they have the same position, they have the same size fragments and have to be the same or related plasmids.

The example here is from a plasmid that entered a hospital, lane 2—lane 1 is a reference—lane 2 is a plasmid that entered a hospital, had not been seen there, entered and circulated widely in bacteria of different species in that hospital beginning in 1976. Lane 2 is from 1976.

It was found repeatedly in bacterial isolates of patients in that hospital until now. It's still there in 1984 and these are a random selection of plasmids from that—containing that plasmid, looked at over—collected and later looked at over that 6-year period, 7-year period up through 1982-83, and what you can see is the plasmid is virtually identical, No. 1, there are so many bands in common that you'd have to believe that it was virtually the same—same ancestral clone, but it does—as it moves on in time, it does evolve; it does generate changes. It loses bits of—it loses parts of the chain here; it gains a chunk of chain somewhere else from another plasmid, and so there are slight variations in its function. It may pick up some new genes; may lose one; slight variations in its function as it moves on in time reflected in—as they have to be—in slight variations in the pattern.

The next slide——

[Slide.]

Dr. O'BRIEN [continuing]. Is a diagram, a more extended diagram, of measurements of this same plasmid and you can see that as it moved on, it gained or lost pieces here and there, but always had so many in common that it was possible to identify it as being related, to belong to the same pedigree of the one that initially came into the hospital.

You will notice—we'll bring this up again—that the last 8 or 10—there's a bracket up above said "no transfer." Most of those had lost the larger top fragment, a fairly big chunk—actually almost about 18,000 bases—and must have lost some of the genes that make the mechanism for transfer to other strains because those could no longer transfer. They could only stay—they still made the strain that carried them antibiotic resistance—resistant, but were not able to move from that to others. They had lost that function.

The next slide——

[Slide.]

Dr. O'BRIEN [continuing]. Brings us to some that we looked at several years ago, looking at the possibility that there was relatedness between antibiotic resistance plasmids in animals—isolated from bacteria in animals and from bacteria from humans. This is a gel, again, that shows plasmids isolated, some of them from ani-

mals and some of them from humans, and the first three on the left—I think you can see that they have their fragments close with minor variations—are from isolates from cattle in Idaho, the first one; in Utah, the second one; and in North Dakota, the third, and I think you can see substantial relatedness, very minor variations between those.

The fourth, lane No. 4, is a human isolate of a Salmonella typhimurium from a human in Massachusetts who was part of an outbreak and I think you can see again minor variations, strong relatedness. The fifth is from a different human in Massachusetts, probably at about the same time, probably the same outbreak, although it was never traced the way Dr. Cohen was able to trace his, and you can see that's an identical plasmid.

No. 6 is a copy of it made in a different way.

No. 7 is another cattle isolate slightly different, this time from Missouri.

No. 8 is a human isolate from Massachusetts, so again, a little bit more variation there, but it matches some of the variants—quite a few of the variants of the cattle isolate.

Lane No. 9 is an entirely different—an entirely different species. This is a Salmonella newport and this is an isolate from a pig in Nebraska, on a farm in Nebraska, No. 9, and No. 10 is the antibiotic resistance plasmid carrying the same antibiotic resistance genes from a human isolate that was part of an outbreak in Wisconsin.

No. 11 is from a human—a human isolate in Massachusetts. It's similar, but you can see it has some extra fragments.

Again, shifting to a different species in No. 12, this is a bovine isolate from California, multiresistant Salmonella dublin in this case—the species was dublin—and No. 13 is a human isolate of Salmonella dublin with the same resistance pattern from a patient, human patient in California, and No. 14 is a—another Salmonella dublin isolate, this time from Indiana, cattle isolate from Indiana, and this one had additional resistance and had another plasmid. I think you can see the additional fragments of the other plasmid that were also present.

This is summarized—the Salmonella data or for the first nine—the type of Salmonella that are shown in the first eight lanes, the Salmonella typhimurium that was so widespread in cattle isolates in different States, and in human isolates in several States that we looked at, the fragments of a larger series of those are summarized on the diagram that follows——

[Slide.]

Dr. O'BRIEN [continuing]. And this shows them—here they are arranged by a computer so that those—something that's very hard to do by eye—but a computer can arrange them so that those with the most fragments in common—closest to one another in the lanes here, and you can see that there is continuous variation.

The last three on the right have the same resistance, but are totally unrelated just by contrast to show you—I think you can see lanes Nos. 52, 53, 54, somewhat related to one another, but virtually no fragments in common with the others, presumably a highly resistant—but also to illustrate the resolving power of the technique—also from Salmonella typhimurium the same species with exactly the same resistance.

I would point out just one other—two other things about this. When you arrange them in this sequence with those most—with most fragments in common closest together, that the sequence along the top, the second row down, if you can read it on the side, Idaho, Ohio, California, Massachusetts—Massachusetts—the State sequence tends to be jumbled. There doesn't seem to be certain types in certain regions, at least from the limited data here, and second, if you look at the—at the listings across the top—again, on the side, they're tipped on their sides—are the letter "a" or the letter "h" for animal isolate or human isolates, you can see that they, too, tend not to be widely segregated by this matching technique, but tend to be jumbled together, animal-animal, human-human, animal-animal-animal, human-human-human, and so on, indicating that there is not widespread separation of the pedigrees of these.

One more thing that I would point out—and I think this may relate to what Dr. Holmberg and Dr. Cohen had talked about—if you look at lanes Nos. 15, 16, 17, 18, 19, and 20—and I think—if you look at about the middle, from top to bottom, at about the middle, you'll see that there are six bands that are just alike there, and in fact, if you looked at them carefully up and down, you would see that all the other bands were exactly alike.

In this continuous evolutionary variation, those were the only six that were absolutely the same. The others had a fragment or two different here and there and those six were all obtained from human isolates in different parts of Massachusetts over about a 6-week period. So they were presumably from some single outbreak; some subclone, small suboutbreak of the whole epidemiology that had spread—we don't know how—to the humans in Massachusetts during that time, but I think it illustrates that where there is in time and geography a reason for believing that the isolates were more closely related, in fact, this is confirmed by their restriction fragments in that instance being exactly the same, and I believe that the ones in Dr. Cohen's paper were either—either that the restriction fragments were exactly the same or within a fragment of one another.

And in this context, I—I would say that that suggests certainly, just on the molecular grounds, a close relatedness.

Thank you.

[The prepared statement of Dr. O'Brien follows:]

ELEMENTS OF ANTIBIOTIC RESISTANCE IN POPULATIONS OF BACTERIA

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A. Elements of Antibiotic Resistance

1. Genetic Code

DNA (desoxyribonucleic acid) carries the information to make the proteins, and the proteins make the cells of all living creatures from single celled bacteria to multibillion celled people. Four kinds of DNA bases, abbreviated as A, T, G and C, are strung together in long chains to form genes. Each sequence of 3 bases (e.g. CGT, ACG etc.) along the chain is the code for one of the 20 kinds of peptides from which proteins are made. A sequence of, for example, 300 DNA bases along one whole gene would encode the specific sequence of 100 peptides along one specific protein chain.

2. Chromosome

Thousands of genes strung together one after another in the extremely long chain of the chromosome encode each of the thousands of specific proteins needed to make a specific living cell. When the cell grows and divides each of the daughter cells gets a copy of the chromosome so that each will have the information to make its own complete set of proteins.

3. Antibiotic Resistance Genes

Antibiotic resistance genes are genes which encode proteins that can destroy one or more of the antibiotics. A strain of bacteria which has one of these genes and makes the corresponding antibiotic-inactivating protein can continue to grow in the presence of (is resistant to) that antibiotic.

4. Emergence of Antibiotic Resistance Genes

Antibiotic resistance genes were vanishingly rare before antibiotics began to be used 40 years ago. There are now more than 3 dozen different kinds, some of them widely distributed among strains of bacteria everywhere, some still quite rare. A new antibiotic may be used for years before a gene encoding resistance to it begins to be noticed. We don't know how they arise. Presumably, use of the antibiotic eventually provides a selection advantage for overgrowth of some obscure strain somewhere which happens to have a gene which encodes the resistance protein or can mutate to do so.

5. Plasmids

In addition to their chromosome some bacteria also carry one or more plasmids. A plasmid is like a little auxiliary chromosome 1/100 to 1/10 the size of the real one. It too is a chain of genes, each with its own sequence of DNA bases encoding its own specific protein, but fewer genes corresponding to its shorter length. Daughter cells get copies of the plasmid as well as of the chromosome.

6. Importance of Plasmids

Plasmids are important to antibiotic resistance for two reasons. One is that most of the antibiotic resistance genes have come to be carried on plasmids rather than on chromosomes. The other is that many plasmids can transfer themselves from one bacterium to another, even to another of a different species. This creates an enormous potential for spread of genes, including antobiotic resistance genes, through bacterial populations. The genes that a strain of bacteria carries on its chromosome are restricted largely to those possessed by that strain's ancestors. The genes on its plasmid, and the plasmid itself, may have been acquired from a bacterial stranger passing through 20 minutes earlier.

B. Resistance in Bacterial Populations

1. Networks of Bacterial Populations

Each of us, human or animal, is a habitat for billions of bacteria belonging to hundreds of strains and dozens of species competing for environmental niches in or on us. We exchange bacteria with one another so that larger groupings of us, such as the patients in one hospital or the cattle in one feedlot, also constitute bacterial ecosystems. These ecosystems ultimately interconnect to form a global bacterial ecosystem through which bacterial strains, plasmids and genes can move.

2. Pathogens and Bystanders

Only a miniscule fraction of these bacteria ever infect anyone. In pursuit of those few, however, we have perturbed large portions of these populations over the past 40 years with a succession of antibiotics. We have to date invented and deployed a dozen or so different antibiotics plus variations, and the bacteria have come up with and counterdeployed largely on plasmids more than three dozen different antibiotic resistance genes.

3. Antibiotic Treatment of a Bacterial Ecosystem

When one of these bacterial ecosystems, one of us for example, is treated with a particular antibiotic and happens to harbor one strain of bacteria with a gene encoding resistance to that antibiotic, that strain, freed of pressure from its now dead competitors, will multiply into some of the competitor's niches. It alone will lack

many of the competitors diverse talents for filling the niches and so will probably fill them poorly and relinquish them quickly after the antibiotic is stopped.

4. The Difference a Transferable Plasmid Makes

If, however, the resistance gene were on a transferable plasmid it might have spread into multiple strains which could more completely fill the niches and then more slowly relinquish them. What a transferable plasmid does then essentially in complicated populations of bacteria is to translate a given amount of antibiotic usage into a wider distribution and more prolonged persistence of a resistance gene than would occur without interstrain or interspecies transfer.

5. Efficiency of Plasmids as Amplifiers of Resistance

Since individual plasmids differ in frequency of transfer, in range of bacterial strains or species to which they can transfer, in number and variety of antibiotic resistance genes carried and in carriage of other genes which might favor their persistence in the absence of antibiotics, it seems clear that they must vary greatly in how much and for how long they amplify prevalence of resistance following a given amount of antibiotic usage; in their efficiency as amplifiers of resistance.

6. Consequences of Resistance Gene Amplification

The more the prevalence of an antibiotic resistance gene is amplified, the greater its chances of becoming inserted on a plasmid (if it isn't already) or of becoming transposed to a second plasmid able to transfer to different kinds of bacteria. Greater prevalence also increases the chances that a resistance gene will become linked to other genes (such as other antibiotic resistance genes) which could further enhance its persistence. Greater prevalence also increases a resistance gene's chances of getting into an infecting strain or a strain that colonizes another animal or human.

7. Predetermination of Antibiotic Effect

From these considerations it seems apparent that the events which ensure in the complex bacterial populations of an animal or human treated with an antibiotic will have been largely predetermined by the type and the distribution of antibiotic resistance genes and plasmids which had come to exist in those populations prior to treatment. And that type and distribution will have been largely the consequence of prior antibiotic treatment of that or other interconnected individuals going back to the beginnings of antibiotic usage.

8. Antibiotics as History

A course of antibiotic therapy is in this sense a true historical event, its consequences being affected by prior events and affecting succeeding ones. A patient with an antibiotic resistant strain of bacteria is part of some epidemic.

C. Tracing Resistance Plasmids and Genes in Bacterial Populations

1. Observation of The Antibiotic Resistance System

The preceeding sketch of what might be called the antibiotic resistance system suggests that actual observation of the system in operation, of the deployment of antibiotic resistance genes, plasmids and strains in the bacterial populations of animals and humans would aid the evaluation of antibiotic usage policy. Antibiotic usage is essential, yet it also can be seen to promote emergence of new resistance genes, to concentrate resistance genes in plasmids, plasmids in bacterial populations, resistant strains at the expense of susceptible ones, and to favor the evolution and subsequently the spread of more efficient resistance plasmids. Policy should preserve essential usage and minimize resistance.

2. Technology for Monitoring Deployment of Antibiotic Resistance

The technology available for monitoring the deployment of antibiotic resistance in bacterial populations of animals or humans ranges from routine antibiotic susceptibility testing of clinical isolates of bacteria to molecular genetic studies of resistance genes or plasmids. The whole range of techniques has to be used in an integrated way. Data from routine testing can detect changes in resistance in vast populations which the more elaborate technologies can selectively confirm and explain.

3. Identification of Plasmids

At the upper middle of this range of technologies are those for identifying plasmids. The central role of plasmids in the spread of resistance makes it important to be able to distinguish one from another and to confirm that two from widely separated places are the same. Since plasmids are long chains of specific sequences of DNA bases, determination of that complete sequence of bases would identify the plasmid as absolutely as determining the complete sequence of words in a novel would identify the novel. This is technically possible now but still too laborious for practical use.

4. Restriction Endonuclease Digestion Analysis

Instead of determining the complete sequence of DNA bases in a plasmid another easier technique called restriction endonuclease digestion analysis can now accomplish basically the same purpose. Restriction endonucleases are remarkable enzymes that recognize a particular sequence of six DNA bases (e.g. GCTCGA) and then cut the DNA chain in two at every place where that particular sequence of 6 bases occurs. An electrical current in a gelatin slab then sorts out by length the segments of the DNA chain left between the cuts so that these lengths can be measured. Two identical plasmids will have identical DNA base sequences throughout their lengths and so will have sets of segments of identical lengths between the cut sites.

5. Analogy of Text Identification Without Reading

The analogy for restriction endonuclease digestion analysis could be, again, the determination that two novels were identical. Instead of reading them, one could scan through (have your word processor do this for you) and note every place in the text where a particular word occurred, for example "there". Then count (have the processor count) how many letters and spaces there are between each such occurrence. That set of interval measurements should be identical if the two novels are identical. The possibility of two different novels having by chance exactly the same intervals is unthinkably small, and the same is true for two different plasmids.

6. Suitability of Plasmids for Restriction Endonuclease Analysis

The relatively small size of plasmids makes them suitable for restriction endonuclease analysis. Techniques exist to extract the plasmid from bacterial cells and leave the larger chromosome behind. Their size also makes it likely that they will have a manageable number (5-20) of cut sites, on the average.

7. Plasmid Evolution

Most plasmids exhibit some evolution over time. They gain or lose segments of DNA chain which seem to be transposed onto them or excised off of them. Sometimes these are large enough to include one or more genes, and their corresponding proteins or functions will be gained or lost, for example resistance to an antibiotic or even the ability to transfer themselves to other bacteria. It appears that sometimes a plasmid which has transferred into and persisted in one strain of bacteria may eventually lose transferability although its cousins in other strains continue to have it. Such evolutionary modifications are reflected, as would be expected, in some variation in restriction endonuclease fragment patterns.

8. Epidemiology Needs Diversity

Although restriction endonuclease analysis is a highly accurate way of establishing identity or similarity between plasmid molecules, it would still ack usefulness for tracing their epidemiology if there were only a small number of different plasmid molecules. Many of the resistance genes, which are much smaller of course, have this limitation because they are so widespread and apparently identical all over the world as to obscure any reconstruction of how they spread.

9. Plasmid Diversity

Fortunately for their use as epidemiological tracers, plasmids appear to exhibit a wide range of diversity. They are apparently large enough and undergo enough molecular evolution to ensure that two plasmids related only in the remote past will have substantially or totally different restriction fragment patterns. This expectation tends to be confirmed by the observation that identical or similar restriction patterns have not been observed in random surveys of plasmids but only in circumstances where there was evidence of close epidemiological relatedness.

10. Plasmid Distinctiveness

The evolution and resulting diversity of antibiotic resistance plasmids also provides useful distinctiveness. One epidemic plasmid showed continuous small fragment variations in copies isolates over several years in widely separated places. However, all of the copies from one state over one month were completely identical, suggesting a subclone involved in a suboutbreak.[1] Improved techniques for mapping the sequence of fragments in a plasmid may allow us to reconstruct the genealogy of the variants.

[1] O'Brien, T.F., Hopkins, J.D., Gilleece, E.S., Medeiros, A.A., Kent, R.L., Blackburn, B.O., Holmes, M.B., Reardon, J.P., Vergeront, J.M., Schell, W.L., Christenson, E., Bissett, M.L., Morse, E.V.: Molecular Epidemiology of Antibiotic Resistance in Salmonella from Animals and Human Beings in the United States. New Engl. J. Med. 307:1-6, 1982.

Mr. GORE. Thank you very much. Could you make copies of these slides available for the record?

Dr. O'BRIEN. Yes, sir.

Mr. GORE. Thank you. We'll hold off on questions.

Our third witness is Dr. Virgil Hays, with the Department of Animal Sciences at the University of Kentucky in Lexington. Dr. Hays, welcome, and please proceed.

[The biographical sketch of Dr. Hays follows:]

VIRGIL W. HAYS

Virgil W. Hays is Chairman, Department of Animal Sciences, University of Kentucky. He received his B.S. degree from Oklahoma State University and his Ph.D. degree in Animal Nutrition from Iowa State University. He served on the faculty of Iowa State University from 1957 to 1967 and joined the research and teaching faculty at the University of Kentucky in 1967. He was named to his present position in 1974. Virgil is a member of several honorary and professional societies including American Society of Animal Science, American Dairy Science Association, Poultry Science Association, American Institute of Nutrition and Council for Agricultural Science and Technology. He has served on numerous boards and committees of state and national organizations including President of American Society of Animal Science in 1978-79. He is a certified specialist in Animal Nutrition by the American Registry of Professional Animal Scientists, and is presently serving as their President-elect. His research specialization includes amino acid and mineral nutrition and more recently he has concentrated on the safety and efficacy of drugs, particularly antibiotics, in animal production.

ANTIBIOTIC RELATED ACTIVITIES

Virgil W. Hays

1. 24 years of research on the efficacy and safety of antibacterial agents as feed additives.

2. Presented invited paper in the 1967 FDA-NAS sponsored symposium on use of drugs in animal feeds.

   Hays, V. W. 1969. Biological basis for use of antibiotics in livestock production. Proceedings of Symposium, The Use of Drugs in Animal Feeds. Publication 1679. National Academy of Sciences, Washington, D.C. pp 11-30.

3. Presented an invited paper at 1978 Canadian Society of Animal Science sponsored symposium on Feed Additive Use of Antibiotics.

   Hays, V. W. and W. M. Muir. 1979. Efficacy and safety of feed additive use of antibacterial drugs in animal production. Can. J. Anim. Sci. 59:447.

4. Co-authored two invited papers presented at 1976 American Society of Animal Science symposium on "Antibiotics in Animal Feeds".

   Langlois, B. E., G. L. Cromwell and V. W. Hays. 1978b. Influence of type of antibiotic and length of antibiotic feeding period on performance and persistence of antibiotic resistant bacteria in growing-finishing swine. J. Anim. Sci. 46:1383.

   Langlois, B. E., G. L. Cromwell and V. W. Hays. 1978a. Influence of chlortetracycline in swine on reproductive performance and on incidence and persistence of antibiotic resistant enteric bacteria. J. Anim. Sci. 46:1369.

5. Invited discussant for American Society of Animal Science sponsored symposium (1974).

   Hays, V. W. 1975. Relationships of antibiotics in animal feeds and salmonellosis in animals and man - discussant. J. Anim. Sci. 40:1236.

6. Presented invited paper at the American Society for Microbiology sponsored symposium on "Antibiotics in Animal Feeds and in Foods for Humans" at Twelfth Interscience Conference on Antimicrobial Agents and Chemotherapy. 1972.

   Hays, V. 1972. Comparison of growth rates of animals receiving antibiotics in feeds and of "pathogen-free" animals not receiving antibiotics.

   Popularized version of the paper later published.

   Hays, V. W. 1973. SPF Hogs: Do they need antibiotics? Hog Farm Management 10:12:30.

7. Chairman of organizing committee for American Society of Animal Science sponsored symposium on Drugs and Feed Additives (1969). Papers published Journal of Animal Science 31:1102-1132.

8. Prepared a commissioned paper for background information for Office of Technology Assessment, Congress of United States, Washington, D.C. Paper was used as background information in preparing their Technical Report entitled, "Drugs in Livestock Feed.

Commissioned paper later published.

Hays, V. W. 1981. Effectiveness of feed additive usage of antibacterial agents in swine and poultry production. The Hays Report. Rachelle Laboratories Inc., Long Beach, Ca.

9. Chaired CAST Task Force in preparing Report No. 88, Antibiotics in Animal Feeds, Council for Agricultural Science and Technology, March, 1981. Ames, Iowa.

10. Numerous other writings in scientific journals and popular press publications on efficacy and safety of antibiotics.

Dr. HAYS. Thank you, Mr. Chairman. I appreciate the opportunity to present some of our research results on the efficacy of antibiotics and relate those results to current concerns.

I am Virgil Hays, professor and chairman of the Department of Animal Sciences at the University of Kentucky and I have been involved in antibiotic research for about 31 years at the present time.

The benefits of antibiotics to the livestock industries have been well documented and numerous review publications are available to verify those benefits. The total aggregate of the benefits have been estimated to be as much as $3½ billion annually, with the primary beneficiary being the consumer.

We at the University of Kentucky have contributed to the evaluation of the numerous antibiotics and chemotherapeutic agents now used in animal production and also those that have been or are being evaluated for potential usefulness. In addition to our work on the animal responses to antibiotics, we have been very much involved in the impact of antibacterial agents on the microflora of the animals and their environment.

Since 1972, we have monitored the level and pattern of resistance in two separate herds of pigs and have used those—pigs from those herds in experiments at a third location. In the control herd, we have used antibiotics continuously, much as a swine producer would use them, except that a portion of the herd has been exposed continuously throughout the life cycle to tetracycline at a level of 50 to 100 grams per ton.

The other herd has had no exposure to any antibacterial agent for therapeutic or subtherapeutic purposes since the project was started in May 1972. This herd is completely isolated from other pigs. Any new genetic material introduced into the herd is by artificial insemination of selected females to provide the required number of males.

All diets have been prepared in the mill on the research farm and no antibiotic-containing feeds have been processed in that mill during the 12-year period. No animal products are included in the diets so there cannot be carryover from one animal to another into these animals.

These two herds have provided information on the development, and persistency, and transfer of antibacterial resistance and, furthermore, they have provided information regarding the impact of the previously proposed restrictions the antibiotic uses would have on antibiotic-resistance bacteria of animal origin as a health hazard to humans.

Following antibiotic withdrawal, the performance of the pigs in the antibiotic-free herd was markedly reduced. Conception rate on first service has declined; sows farrowed fewer pigs; fewer pigs survived to weaning; and the pigs were smaller at weaning.

Numerous other problems have been encountered since antibiotics were discontinued. A higher proportion of the pigs do poorly, resulting in more variable, as well as a longer time to reach market weight. There has been an increase in the incidence of mastitis, metritis and agalactia of the sows, and there has been a greater incidence of lameness and joint problems in the pigs. There has been greater—on several occasions, the pigs have had severe skin lesions attributed to staphylococcal infections.

Two recent outbreaks of diarrhea were diagnosed as porcine proliferated enteritis with Campylobacter being diagnosed as the causative organism. Conversely, we have not encountered similar or other major health problems in the continuous antibiotic herd.

Some will counter with the argument that no one has proposed a complete ban on antibiotic usage and that these results would not be useful in evaluating the effects of restricted antibiotic use. However, the microbiological data must be considered in evaluating the effectiveness of alternatives other than a complete ban.

We have monitored the level and pattern of antibiotic resistance in enteric bacteria at periodic intervals during the 12 years. Initially, the enteric bacteria of the two herds did not differ greatly in level or pattern of resistance. As one would expect, the level of antibiotic resistance and levels of multiple resistance are higher in the control herd. In that herd, tetracycline resistance in the fecal coliform populations has remained high, averaging more than 90 percent of the organisms being resistant to that antibiotic.

Tetracycline resistance of the fecal coliforms in the antibiotic-free herd has declined from the high level of about 90 percent, but the resistance level still fluctuates between 20 and 55 percent, even though these animals have had no exposure to antibiotics for a 12-year period now and it's more than five-generation turnover of the pig herds.

We have monitored the resistance to 14 antimicrobial agents and the fecal coliforms on the average in this antibiotic-free herd are resistant to 1½ to 2 of those agents.

We find that the level of antibiotic resistance is related to age of animals with organisms from younger pigs having a higher level of resistance than those of more mature animals, even though they are coming—the pigs are coming from the more mature animals.

After 11 years of no antibiotic exposure, approximately 50 percent of the fecal coliforms from pigs less than 6 months of age were resistant to tetracycline and, on the average, were resistant to 2.9 of the 14 agents tested. In more mature pigs, that is, 6 months of age or older, the level of tetracycline resistance was about 25 percent and, on the average, the fecal coliforms were resistant to 1½ agents.

We have found that stressing pigs by transporting them to another location will increase level of resistance and will also increase the shedding of lactose-negative coliforms. These effects are very obvious when the travel is quite distant, but similar, though smaller in magnitude, effects are noted when the animals are transported less than 10 miles.

For example, pigs were sampled prior to and after being transported 200 miles. The level of tetracycline resistance—and these are pigs from the antibiotic-free herd—increased from 40 percent to a level of 80 percent as a result of the stress of moving. Several days were required for the level of resistance to return to the previously lower level. Exposure of the animals to therapeutic levels of antibiotics will markedly raise the level of resistance and a long period of time is required for the resistance levels to return to the pretreatment level.

In an experiment replicated five times, we found that exposure of animals to subtherapeutic levels of gram-positive spectrum antibiotics also resulted in increased levels of tetracycline resistance. The results from our studies make it very clear that the previous proposal from FDA for restricting feed additive use of subtherapeutic levels of penicillin and tetracycline would have very little, if any, impact on the levels and patterns of antibiotic resistance in food-producing animals and the resulting exposure of humans to resistant bacteria of animal origin.

For livestock producers to approach the care we have exercised in avoiding antibiotic exposure would require a complete ban of all antibiotics and other antibiotic agents. Periodic exposure to prophylactic or therapeutic levels of antibacterials would result in high levels of resistance, and in a production environment, that resistance is very slow to decline. The results of the Seattle-King County study are very supportive of the conclusions we have drawn from our experiments.

Antibiotic resistance levels of Campylobacter jejuni associated with processing plants and retail meats were as high or higher in poultry products than for other meats. Since the introduction of the ionophore antibiotics to control coccidiosis in 1971, there has been little subtherapeutic use of tetracyclines or penicillin in broiler production. Furthermore, broiler production and processing and the manufacturing of broiler feeds are largely separated from any aspect of swine and beef production. Thus, in essence, we have experienced a 10-year, large-scale test on the impact of the proposed actions and found it to be nil.

In 1971, Great Britain implemented a ban on subtherapeutic use of tetracyclines in animal production. This action was taken after considerable debate and was greatly influenced by antibiotic-resistant Salmonella infections in humans in the mid-1960s, which appeared to be directly related to similar infections in calves. Antibi-

otics were not approved as feed additives for calves at that time, nor previously. Thus, earlier implementation of the Swann Committee recommendations would have had no apparent impact on that particular epidemic, nor did it prevent a similar—prevent a similar epidemic later, as reported by Rowe in 1979. Dr. Rowe, Director of the Central Public Health Laboratory in London, participated in the July 19–20 International Symposium on Salmonella in New Orleans. He was quoted in Food Chemical News as follows:

> The British increase in the cases of salmonellosis caused by multiple drug-resistant forms of Salmonella typhimurium is totally due to injudicious use of antibiotics in animal husbandy.

If one accepted this sweeping, but unsubstantiated, conclusion, then one would logically conclude that the prohibition of subtherapeutic use in animals of those antibiotics used in human medicine has had no impact on the situation in Great Britain.

Smith reported a slight decrease in tetracycline resistance of Escherichia coli, but the number of pigs excreting these organisms did not change during the 4-year period after implementation of the Swann report recommendations. Our research experiences would support this lack of an impact, but we certainly would not agree that multiple drug-resistant Salmonella in humans is totally related to drug use in animals.

The recent CDC report on the Salmonella newport epidemic in Minnesota and South Dakota has been highly publicized and proclaimed as the direct link or smoking gun that ties feed additive use of tetracyclines in beef cattle to serious human health problems. The authors correctly acknowledge that the organism was not found on that beef farm or in ground beef. They further acknowledge that the resistance pattern of the Salmonella newport most likely did not develop on that farm. The thesis presented to the public is as follows: The organism entered that group of beef cattle by some means, possibly a stray calf from a neighboring farm, and the use of tetracycline gave the Salmonella organism the selective advantage for rapid proliferation. In reality, if tetracycline was used with any regularity on that farm, the tetracycline-resistant Salmonella would have had little, if any, selective advantage because of its tetracycline resistance as the majority of the resident gram-negative organisms would have already been resistant to tetracycline.

If that particular organism did gain entrance to that beef herd, a selective advantage would have been provided equally as likely by the use of a gram-positive spectrum antibacterial agent, a change in the diet of animals, a disruption of feed intake triggered by inclement weather or the stress of transporting those animals to market.

One may say these are mere speculations, but we have research data to support each of them as factors capable of triggering the proliferation of a previously asymptomatic infection.

I do not wish to leave the impression of being unaware of the importance of bacterial contamination of animal products. There is no question about the significance of Salmonella and Campylobacter being a human health problem, and food-producing animals serve, along with 43 million pets, 225 million humans and countless mil-

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lions of wildlife as a part of the total Salmonella Campylobacter reservoir.

There are very serious questions, however, regarding the impact of antibiotic usage in animals on antibiotic resistance in humans. Certainly there are problems and we need to develop means for markedly reducing or completely eliminating bacterial contamination. An earlier CDC report indicates that there are added risks associated with raw meats and milk. Thus, using pasteurized milk and proper handling and cooking of meats are important precautions for preventing food-borne illness.

Another useful means of reducing the health risks from bacterial contamination of animal products and other foods is through public education on personal hygiene of foodhandlers and appropriate cooking and handling techniques. Such mundane approaches to preventing illness do not make media headlines; neither do they greatly add to the food costs.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Hays follows:]

ANIMAL PRODUCTION AND HUMAN HEALTH IMPLICATIONS OF ANTIBIOTICS IN ANIMAL FEEDS

The efficacy of antibiotics in improving rate and efficiency of growth has been well documented by many researchers and has been extensively reviewed (Hays, 1977; CAST, 1981). A comprehensive summary involving 937 experiments and more than 20,000 pigs is presented in table 1. Note that the magnitude of the response is greater for the younger animals and declines as the animal matures. For the most part, this is based on data from research units. Such overall summaries markedly underestimate the total benefits derived from antibiotics for three reasons: (1) it pools the data for the more as well as the less effective antibiotics; (2) it takes into account growth rate and feed conversion but does not include reduction in mortality or improved reproductive performance; and, (3) the magnitude of the responses is smaller in the experiment station environment than in commercial production unit environments. This latter reason is adequately illustrated by the data presented in table 2. By pooling a large number of observations, to at least partially overcome the biological variation associated with small experiments, one can illustrate that the response to antibiotics by young pigs in production units are nearly twice that observed in Experiment Station units.

In discussing the potential adverse effects of antibiotics, one must also consider the beneficial effects. Improved performance of the animals and reduced mortality are definite benefits and the total aggregate of these benefits to all of animal agriculture is very substantial and has been estimated to be as much as a $3.5 billion per year reduction in food to the U.S. consuming public (CAST, 1981).

In addition to our work on the animal responses to antibiotics, we have been very much involved in the impact of antibacterial agents on the microflora of the animals and their environment. Since 1972 we have monitored the level and patterns of resistance in two separate herds of pigs and have used pigs from these herds in experiments conducted at a third location. In the control herd, we have used antibiotics much as a swine producer would except that a portion of the herd has been continuously exposed to tetracycline antibiotics at a level of 50 to 100 grams per ton of feed. The other herd, a Specific Pathogen Free herd located at our Princeton, Kentucky Experiment Station, has had no exposure to any antibacterial agent for therapeutic or subtherapeutic purposes since the project was started (May, 1972). This herd (antibiotic-free herd) is completely isolated from other pigs. Any new genetic material is introduced into the herd by artificial insemination of selected females to provide the required number of males. All diets have been prepared on the research farm and no antibiotic containing feeds have been processed in that mill. No animal products are included in the diets.

These two herds have provided information on development, persistency and transfer of antibacterial resistance; and, furthermore, they have provided information regarding the impact the previously proposed restrictions of antibiotic usage would have on antibiotic resistant bacteria of animal origin as a health hazard to humans.

Following antibiotic withdrawal, the performance of pigs in the antibiotic-free herd was markedly reduced (Langlois et al., 1978 a, b). Conception rate on first service declined (91 percent vs. 84 percent), sows farrowed fewer pigs (10.9 vs. 10.1), fewer pigs survived to weaning (8.9 vs. 7.5), and the pigs were smaller at weaning (12.1 vs. 11.5 lb.).

Numerous other problems have been encountered since antibiotics were discontinued. A higher proportion of the pigs do poorly (runt pigs) resulting in more variable as well as an overall increase in length of time to reach market weight. There has been an increase in the incidence of mastitis, metritis and agalactia, 10 vs. 26 percent of sows affected. There has been a greater incidence of lameness and joint problems. On several occasions, the pigs have had severe skin lesions attributed to staphylococcal infections. Two recent outbreaks of diarrhea were diagnosed as porcine proliferated enteritis with Campylobacter diagnosed as the causative organism. Conversely, we have not encountered similar or other major health problems in the control (countinuous-antibiotic) herd.

Some will counter with the argument that no one has proposed a complete ban on antibiotic usage, and that these studies would not be useful in evaluating the effects of restricted antibiotic use. However, the microbiological data must be considered in evaluating the effectiveness of alternatives other than a complete ban. We have monitored the level and pattern of antibiotic resistance in enteric bacteria at periodic intervals during the past 12 years. Initially, the enteric bacteria of two herds did not differ greatly in level or pattern of resistance. Though there had been no specifically planned use of antibiotics and no one antibiotic had been used continuously at either location, antibiotics were used experimentally or as a swine producer would use them.

As one would expect, the levels of antibiotic resistance and levels of multiple resistance are higher in the control herd. In that herd, tetracycline resistance in the fecal coliform populations has remained high, averaging more than 90 percent. Tetracycline resistance of the fecal coliforms in the antibiotic-free herd has declined from the high level of above 90 percent; but, the resistance level still fluctuates between 20 to 55 percent even though these animals have had no exposure to antibiotics for five or more generations. We have monitored the resistance to 14 antimicrobial agents; and, the fecal coliforms, on the average are resistant to 1.5 to 2.0 of those agents (table 3).

We find that the level of antibiotic resistance is related to age of animal, with organisms from younger pigs having a higher level of resistance than those of more mature animals.

After 11 years of no antibiotic exposure, approximately 50 percent of the fecal coliforms from pigs less than six months of age were resistant to tetracycline; and, on the average were resistant to 2.9 of the 14 agents tested. In more mature pigs (6 months or older) the level of tetracycline resistance was about 25 percent; and, on the average, the fecal coliforms were resistant to about 1.5 agents.

We have found that stressing pigs by transporting them to another location will increase the level of resistance and will also increase shedding of lactose-negative coliforms. These effects are very obvious when the travel is quite distant; but, similar, though smaller in magnitude, effects are noted when animals are transported less than 10 miles. For example, pigs were sampled prior to and after being transported 200 miles. The level of tetracycline resistance increased from 40 percent to a level of 80 percent as a result of the stress of moving. Several days were required for the levels of resistance to return to the previously lower level.

Exposure of the animals to therapeutic levels of antibiotics will markedly raise the level of resistance, and a long period of time is required for the resistance levels to return to the pretreatment level. In an experiment replicated five times (Langlois et al. 1978b), we found that exposure of animals to subtherapeutic levels of gram-positive spectrum antibiotics also resulted in increased levels of tetracycline resistance.

The results from our studies make it very clear that the previous proposal [The Food and Drug Administration, Fed. Reg. 42:43770 (Aug. 30, 1977) and Fed. Reg. 42:52645 (Oct. 21, 1977)], for restricting feed additive use of subtherapeutic levels of penicillin and tetracycline would have very little, if any, impact on the levels and patterns of antibiotic resistance in food producing animals and the resulting exposure of humans to resistant bacteria of animal origin.

For livestock producers to approach the care we have exercised in avoiding antibiotic exposure would require a complete ban of all antibiotics and other antibacterial agents. Periodic exposure to prophylactic or therapeutic levels of antibacterials would result in high levels of resistance and, in a production environment, that resistance is very slow to decline.

The results of the Seattle-King County (Nolan et al. 1984) study are very supportive of the conclusions we have drawn from our experiments. Antibiotic resistance levels of the Campylobacter jejuni associated with processing plants and retail meats were as high or higher in poultry products than for other meats. Since the introduction of the ionophore antibiotics to control coccidiosis (1971), there has been little subtherapeutic use of tetracyclines or penicillin in broiler production. Furthermore, broiler production and processing and the manufacturing of broiler feeds are largely separated from any aspects of swine and beef production. Thus, in essence, we have experienced a 10 year, large scale test on the impact of the proposed actions and found it to be nil.

In 1971, Great Britain implemented a ban on subtherapeutic use of tetracyclines in animal production. This action was taken after considerable debate and was greatly influenced by antibiotic resistant Salmonella infections (*S. typhimurium* phage type 29) in humans in the mid-1960's, which appeared to be related to similar infections in calves (Anderson, 1970). Antibiotics were not approved as feed additives for calves at that time nor previously. Thus, earlier implementation of the Swann Committee (1969) recommendations would have had no apparent impact on that particular epidemic, nor did it prevent a similar epidemic later (Rowe et al., 1979).

Dr. B. Rowe, Director of the Central Public Health Laboratory, London, participated in the July 19-20 International Symposium on Salmonella in New Orleans. He was quoted in Food Chemical News (Aug. 6, 1984, page 17) as follows: "the British increase in cases of salmonellosis caused by multiple-drug-resistant forms of *S. typhimurium* is totally due to injudicious use of antibiotics in animal husbandry". If one accepted this sweeping but unsubstantiated conclusion, then one would logically conclude that the prohibition of subtherapeutic use in animals of those antibiotics used in human medicine has had no impact on the situation in Great Britain. Smith (1977) reported a slight decrease in tetracycline-resistant Escherichia coli, but the number of pigs excreting these organisms did not change during the 4-year period after implementation of the Swann Report recommendations by the British Government. Our research experiences would support this lack of an impact; but, we certainly could not agree that multidrugresistant Salmonella in humans is totally related to drug use in animals.

The recent report (Holmberg et al., 1984) on the Salmonella newport epidemic in Minnesota and South Dakota has been highly publicized and proclaimed as the "direct link" or "smoking gun" that ties feed additive use of tetracyclines in beef cattle to serious human health problems. The lay public or even the journalists could not be expected to give proper recognition to the speculations in that journal paper wich were required to link the infective Salmonella to that particular beef farm and even further to conclude that subtherapeutic use of antibiotics either resulted in the development of the resistance pattern or resulted in selecting for the organism. The scientists, however, writing the paper or editorializing on the paper should have been more objective in their approach. The authors correctly acknowledge that the organism was not found on the beef farm or in ground beef. They further acknowledge that the resistance pattern (tetracycline-ampicillin-carbenicillin) of the S. newport organism most likely did not develop on that farm. The thesis presented to the public is as follows: the organism entered that group of beef cattle by some means, possibly a stray calf from a neighboring farm, and the use of tetracycline gave the Salmonella organism the selective advantage for rapid proliferation. In reality, if tetracycline was used with any regularity on that farm, the tetracycline resistant Salmonella would have had little, if any, selective advantage because of its tetracycline resistance, as the majority of the resident gram-negative organisms would have been resistent to tetracycline.

If that particular organism did gain entrance to that beef herd, a selective advantage could equally as likely be provided by the use of a gram-positive spectrum antibacterial agent, a change in the diet of the animals, a disruption of feed intake triggered by inclement weather, or the stress of tansporting those animals to market.

One may say the above are mere speculations also; but, we have research data to support each of them as factors capable of triggering the proliferation of a previously asymptomatic infection.

I do not wish to leave the impression of being unaware of the importance of bacterial contamination of animal products. There is no question about the significance of Salmonella and Campylobacter jejuni being a problem in human health, and food producing animals serve along with pets, humans and wildlife as a part of the total Salmonella-Campylobacter reservoir. There are very serious question, however, regarding the impact of antibiotic usage in animals on antibiotic resistance in humans. Certainly, there are problems, and we need to develop means for markedly reducing or completely eliminating bacterial contamination. An earlier CDC report

(Holmberg et al., 1984b) indicates there are added risks associated with raw meats and milk. Thus, using pasteurized milk and proper handling and cooking of meats are important precautions for preventing food borne illnesses. There is a need for a concentrated effort to find economical means of reducing Salmonella and Campylobacter contamination.

Another useful means of reducing the health risks from bacterial contaminants of animal products and other foods includes public education on personal hygiene of food handlers and appropriate cooking and handling techniques. Such mundane approaches to preventing illness do not make media headlines, neither do they add greatly to food costs.

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Table 1. Response of pigs to subtherapeutic levels of antibiotics[1]

	Control	Antibiotic	Improvement, %
Starter phase (15-57 lb)			
Average daily gain, lb	.86	1.01	16
Feed/gain	2.32	2.16	7
Grower phase (37-108 lb)			
Average daily gain, lb	1.30	1.45	11
Feed/gain	2.91	2.78	5
Grower-finisher phase (44-189 lb)			
Average daily gain, lb	1.50	1.56	4
Feed/gain	3.37	3.30	2

[1]Data from 378, 280 and 279 experiments, involving 10,023, 4,783 and 5,666 pigs for the three phases, respectively (Hays, 1977).

Table 2. Comparison of response to antibacterial agents by pigs in experiment station and production unit environments[1]

Location	No. Experiments	Improvement from Antibiotics, %[2] Daily gain	Feed/gain
Experiment station research units	128	16.9	7.0
Production units	32	28.4	14.5

[1]Data on 12,000 pigs from 15 to 57 lb. (Hays, 1977).

[2]Chlortetracycline-penicillin-sulfamethazine, tylosin-sulfamethazine, tetracyclines and carbadox.

Table 3. Tetracycline resistance in fecal coliforms of pigs in antibiotic-free herd (no antibiotics since 1972)

Age of pig, months	No. isolates	Tetracycline resistance %	Multiple resistance[1] no.
All isolates (1972-1982)			
2-6	977	73	2.5
7-11	358	26	1.1
12-23	701	35	1.5
>23	370	30	1.5
Samples, March '83			
2-6	161	55	2.9
7-11	51	24	1.6
12-23	47	26	1.4
>23	21	24	1.7

[1]Average number of antibacterials to which fecal coliforms were . . .

Mr. GORE. Thank you. We'll hold off on our questions until we've heard from Dr. Sabath.

Dr. Leon Sabath is professor of medicine at the University of Minnesota in Minneapolis. We're delighted to have you here and please proceed.

[The biographical sketch of Dr. Sabath follows:]

LEON DAVID SABATH

Born: Savannah, Georgia July 24, 1930

Divorced; 3 children

1952	A.B. Harvard College (magna cum laude)
1956	M.D. Harvard Medical School
1956 - 1957	Intern, Peter Bent Brigham Hospital
1957 - 1959	Captain, Medical Corps, U.S. Army (Reserve)
1959 - 1960	Assistant Resident, First (Columbia) Medical Division and Chest Service, Bellevue Hospital, New York City
1960 - 1962	Research Fellow in Medicine, Harvard Medical School and Research Fellow, Thorndike Memorial Laboratory, Boston City Hospital
1962 - 1963	Senior Assistant Resident in Medicine, Peter Bent Brigham Hospital, and Assistant in Medicine, Harvard Medical School
1963 - 1965	Research Associate, Sir William Dunn School of Pathology, University of Oxford, England, under tenure of a special Research Fellowship, National Institute of Allergy & Infectious Diseases, U.S. Public Health Service
1965 - 1967	Associate in Medicine, Harvard Medical School, and Research Associate, Thorndike Memorial Laboratory, Boston City Hospital
1965	Clinical Associate, II & IV (Harvard) Medical Services, Boston City Hospital
1966	Clinical Assistant, II & IV (Harvard) Medical Services, Boston City Hospital
1967 - 1968	Assistant Physician, II & IV (Harvard) Medical Services, Boston City Hospital
1967 - 1974	Assistant Physician, Thorndike Memorial Laboratory, Boston City Hospital
1968 - 1974	Attending Physician, West Roxbury Veterans Administration Hospital
1968 - 1971	Assistant Professor of Medicine, Harvard Medical School
1969 - 1974	Associate Visiting Physician, II & IV (Harvard) Medical Services, Boston City Hospital
1971 - 1974	Associate Professor of Medicine, Harvard Medical School

L. D. Sabath

1972 - 1974	Consultant for Infectious Diseases, New England Deaconess Hospital
1974 - 1983	Professor of Medicine and Head, Section on Infectious Diseases, University of Minnesota Medical School
1975, 1976	Visiting Lecturer on Medicine, Harvard University
1983 -	Professor of Medicine, Section on Infectious Diseases, University of Minnesota Medical School

Awards:
- 1963 Mosely Traveling Fellowship, Harvard Medical School (declined to accept Special Fellowship, NIAID)
- 1963-65 Special Fellowship, National Institute of Allergy and Infectious Diseases
- 1968-72 Career Development Award, National Institute of Allergy and Infectious Diseases

Dr. SABATH. Thank you, Mr. Chairman. I am Lee Sabath, professor of medicine at the University of Minnesota, where my work is in both clinical medicine dealing mainly with infectious diseases and resistance of bacteria to antibiotics.

I'm especially pleased to be in this room surrounded by reminders of the moon and space and bring us back to diarrhea in humans and germs in barnyard refuse.

I'm especially glad to also be able to follow the preceding three speakers because Dr. Cohen beautifully summarized the article by himself and several others in the New England Journal of Medicine concerning the possible dangers of antibiotics in animal feeds related to antibiotic-resistant bacteria causing diseases in man. And in the letter from Mr. Gore, I was asked to comment on three things and I'll do that. Namely: the article itself; a few words about Salmonella; and something about bacterial resistance to antibiotics.

Now, the article has two strong points.

Mr. GORE. Dr. Sabath, if I could interrupt you just briefly. I've noticed we have several people standing who don't have seats. There may be one or two seats over here and you're welcome to fill in this first row if you care to and——

Mr. GLICKMAN. But you can't ask questions.

Mr. GORE. But you can't ask questions of the witnesses. [Laughter.]

That's the only stipulation. But go ahead, Dr. Sabath. Sorry to interrupt.

Dr. SABATH. Certainly. Well, the two major strong points of the article in my estimation are some beautiful detective work relating diarrheal disease in—it turned out to be 18 patients—to a dairy herd in South Dakota; and the second strong point—and that was gone into in some detail by Dr. Cohen—was the beautiful microbiology, very clearly and unmistakably showing that those germs causing disease in those humans is almost certainly exactly the same as in that dairy herd in South Dakota.

In fact, on the way to the airport yesterday, I picked up my report from the CDC, the weekly Morbidity and Mortality Report—in 1983, actually, that same germ that was causing the disease was actually—the Salmonella newport—was the fourth most common

Salmonella for 1983, over 3,000—sorry, over 2,000 isolates from humans, and so Dr. Cohen's work showing it was exactly the same one was a beautiful piece of work. Those are the two strong points.

However, there are some very important weak points and I'd like to mention three of them. First, as Dr. Hays has pointed out, there's absolutely no evidence whatsoever that those organisms were ever in the hamburger meat or beef from the suggested route from the dairy farm to those humans. Not a single isolate from beef or from the soil on that farm or manure on that farm or any of the streams on that farm. So that it has not been established that the hamburger was involved at all.

The second weakness in my estimation is no extensive data about other possible routes by which those organisms—and I think the beautiful microbiology suggested it was those organisms—but no work reported on other possible routes on how those Salmonella might have gotten from that dairy farm to the humans, such as person-to-person contact, and in fact, in the article, it's clearly stated that 3 of those 18, in fact, probably got their infection by human-to-human contact and not by any food product at all.

How might that be? Somebody working on the dairy farm might have been involved in the beef-producing place or in transport of meat or other material feeds or whatnot used on the dairy farm and also on the beef-production place.

Perhaps even more frightening, but possible, is the possibility that an animal from that dairy farm somehow was sold as beef and distributed through that network, and that is possibly what led to the disease in the humans. We are told that one calf on that dairy farm actually died of the Salmonella infection and those germs were isolated, in fact, from that dead calf. So that point is not as adequately demonstrated as I would have liked to have seen.

And then the third point, and that is the one that Dr. Hays made, a very striking weak point of the article in their conclusion is that it's the use of subtherapeutic levels of antibiotics in feed that led to the promotion and selection of resistant organisms in the current setting. As Dr. Hays pointed out, with the resistances shown and the antibiotics used, that's absolutely unsupportable.

What is not mentioned at all in the article, and probably is of great importance here, is the use of antibiotics at high levels for therapy in sick animals, and that's exactly what happened on that dairy farm. There was an outbreak of diarrheal disease and high levels of antibiotics were used for treating of those animals. That's clearly a selective influence on the prevalence of resistant bacteria and that wasn't emphasized at all in the article. So those are the three weak points.

Now, I'd like to just turn and say a few words about the—what does select resistant bacteria in the environment and I think absolutely no one would question the fact that antibiotics anywhere exert a selective effect on what kind of bacteria are going to survive, whether it's in a laboratory dish or in our environment, and there are four important selective facts: One is the use of antibiotics for therapy in man; second is use of antibiotics for preventing infection in man, and I believe this committee's going to hear more about that tomorrow; then also use of antibiotics for therapy in veterinary medicine, and in my mind, that's one of the key issues in

the outbreak that appears to have stimulated the convening of this committee; and the third—I'm sorry, the fourth is the use of antibiotics in low levels to promote growth in animal feeds. All four of those are key issues in the selection of resistant antibiotics.

Now, I would like to add just this word about Salmonella, that it's an especially key organism to focus on because it's one of the few organisms that come from animals but actually may persist for long periods in man, and that's a fact, so Salmonella really deserve our attention.

Now, the concern is, does the use of antibiotics in these low levels lead to the prevalence or increase of antibiotic resistance that poses a threat to man, and there are data on that and I'd like to show that with two slides, if I may.

[Slide.]

Dr. SABATH. Actually we can skip over that first slide there which simply is from the article that Dr. Cohen and others wrote, but let's go on to the next one.

[Slide.]

Dr. SABATH. Which is four panels from work by Atkinson and Lorian and, although you can't read the fine points, their point—their conclusion is easily visible to all of us. Namely, that those four graphs show changes in antibiotic susceptibility for important pathogens isolated from man between 1971 and 1982. And as you can see, the vast majority of those lines are straight across, showing there has been no major change in antibiotic resistance in those 12 years shown, 1971 to 1982, in bacteria from patients in American hospitals. So, in fact, there has not been a major increase in antibiotic resistance in those organisms shown.

Now, the next point, which I'd like to turn to the next slide with.

[Slide.]

Dr. SABATH. Is what happens—and that's—we can skip over that—that's also from that article—is what happened in Britain when they did ban the use of antibiotics in low levels for feed in man. This is from a paper by Linton, which is mentioned in the bibliography I handed out, and is—he shows in this slide between 1971 and 1979—the letters across the top show different antibiotics—and as you can see they're years shown and the numbers are the percent resistance of Salmonella to those antibiotics. There has been no decrease—the first column there is for sulphonamides; the second is for streptomycin, where there—I should correct myself. There has been a little decrease with streptomycin resistance, but for all the other antibiotics, there's actually been a slight increase, even though the use of antibiotics in subtherapeutic use was banned in Britain.

Now, how could this happen without that selective force? Well, the obvious thing is those animals were receiving antibiotics in high levels for therapy of their infection.

Next slide.

[Slide.]

Dr. SABATH. Is also from the work of Linton and simply breaks this down, A, B, and C standing for different types of Salmonella. Now, if we could turn that off for a moment, I'd actually like to read from that article, which I believe is No. 5 in the bibliography I handed out from Linton, who said that, "The question why has

Swann failed"—and that refers to the Swann report which led to the banning of the use of antibiotics in Britain. Linton says, "The question why has Swann failed is misdirected. Apart from the fact that Swann's recommendations were not given the chance to prove themselves, they are unlikely to have succeeded in the absence of simultaneous restriction on the prophylactic and therapeutic use of antibiotics in both animals and man. Partial restriction in one area of use will not avoid the occurrence of antibiotic resistance arising from other uses. I believe that Swann succeeded by being a failure. The report focused attention on the growing problems of antibiotic resistance and, by its failure, has forced the opinion that the control of infections by multiply resistant pathogens must be pursued along conventional epidemiologic lines and not solely by imposing more stringent restrictions on antibiotic use."

Now, in conclusion, I'd like to point out that I commented on the article in the New England Journal which stimulated this attention, which reported on Salmonella infections of 18 humans, which beautifully traced it back to a dairy farm. Second, although the article didn't really focus on the key epidemiologic point, the basic point is the danger of spread from animals to humans. Although the article failed to show that it was actually in the hamburger; whether it was spread on the hands of other individuals, whether it was infected animals somehow finding their way into the chain; whether it was in the runoff of water; somehow there was a transmission of those organisms from infected animals to man.

I've also pointed out that in spite of the use of antibiotics in animal feeds at low levels, and also in therapy in man and animals, there's been no marked increase in antibiotic resistance in this country in major pathogens over the 12 years shown in the data I presented.

We don't have to speculate about what would happen if antibiotic use in animal feeds was prohibited because with the example we've seen from Britain showed that it did not make a difference. Obviously the conclusion—and I think it's an important one—is that more work is needed on our basic information about antibiotic resistance, which is an important problem, and how to prevent its spread.

I'd like to add just one last point before closing, that among our problems in many antibiotic-resistant bacteria, one in which there has been a clear increase in resistance has been with the organism called staphylococcus epidermidis. There's been a clear increase in resistance of that organism and it's never been suggested that that organism comes from food products or animals.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Sabath follows:]

Statement by L.D. SABATH, M.D., of University of Minnesota

on

ANTIBIOTICS IN ANIMAL FEEDS AND THEIR POSSIBLE IMPACT ON ANIBIOTIC-RESISTANT ORGANISMS INFECTING HUMANS

Prepared for hearing by Subcommittee on Investigations and Oversight of the COMMITTEE ON SCIENCE AND TECHNOLOGY of the U.S. House of Representatives

Scheduled for December 18, 1984
Washington, D.C.

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Minneapolis, Mn. 55455

ABBREVIATED SUMMARY

A recent article by Holmberg and others (Sept. 6, 1984, New England Journal of Medicine) in which excellent epidemiologic and microbiologic methods were used, traced the origins of diarrheal disease due to Salmonella newport from 18 patients in 4 Midwestern states to a dairy farm in South Dakota. They concluded that 1) contaminated beef, originating from a beef feeder lot next to the dairy farm was the vehicle by which the Salmonellae were transmitted to humans, and 2) the practice of adding subtherapeutic amounts of antibiotic to animal feeds for growth promotional purposes was responsible for the emergence and selection of antibiotic resistant organisms, such as these.

Neither conclusion is substantiated by facts. No Salmonella newport were isolated from beef, the soil or environs of the feeder lot, and the exact means of transmission remains unproven. More importantly, the second conclusion is totally unjustified because the evidence does point to the resistant Salmonella coming from the dairy farm, where the use of subtherapeutic low dose antibiotics in animal feeds is prohibited. Whatever selection pressure antibiotics may have had was by their therapeutic use (high level) for treating diarrheal disease in the dairy animals!

In the United States, where subtherapeutic use of antibiotics in animal feeds continues, there has been no marked increase in antibiotic resistance coming directly or indirectly from farm animals. In Britain, where such use has been prohibited since 1971 (following the Swann Committee Report) there has been no decline (possibly an increase) in antibiotic resistance of Salmonellae.

Although antibiotic resistance of bacteria remains an important problem, there is no evidence to prove antibiotics in animal feed pose a threat to human welfare. The selective prossure resulting from antibiotic use in treating and preventing human infections, and in treating veterinary infections is probably a more important factor in selecting and maintaining resistant bacteria in our environment.

LEON DAVID SABATH, M.D.
A Brief Biographical Sketch

Dr. Sabath is Professor of Medicine at the University of Minnesota Medical School in Minneapolis, Minnesota, where he teaches medicine, practices internal medicine and the specialty of infectious diseases at the University of Minnesota Hospitals, and he is also engaged in research, mainly concerned with various aspects of bacterial resistance to antibiotics, and how to best use antibiotics in patients.

He is a Diplomate of the American Board of Internal Medicine and a Diplomate of the Subspecialty of Infectious Diseases. He is a Fellow of the American College of Physicians and a Fellow of the Infectious Diseases Society of America, and a member of various other professional societies.

He received the A.B. (magna cum laude) at Harvard, and his M.D. at Harvard Medical School in 1956. His clinical training in medicine was received in Boston (Peter Bent Brigham Hospital) and New York (Bellevue Hospital). He was a Fellow in Infectious Diseases under the direction of Maxwell Finland at the Harvard Medical Unit at Boston City Hospital, and he spent two years at the University of Oxford (England) under the direction of Sir Edward Abraham. Dr. Sabath then served on the faculty of Harvard Medical School for nine years before moving to Minnesota ten years ago, as Professor of Medicine. He has published 157 scientific papers, chapters, and reviews, mainly on the subjects of bacterial resistance to antibiotics and how to best use antibiotics in patients.

He organized and chaired a symposium entitled "Antibiotics in Animal Feeds" in 1972, for the Interscience Conferance on Antimicrobial Agents and Chemotherapy, while a member of the program Committee of that organization.

EXTENDED ABSTRACT OF DR. SABATH'S REMARKS

The possibility that antibiotics in animal feeds are a hazard and lead to the development of antibiotic resistant organisms which then spread to humans has been, and remains, a controversial subject. A recent article by Holmberg and others has been quoted as supplying the missing link to prove the danger. The article in no way shed light on the role of antibiotics in animal feeds as apossible danger to humans. The article reports beautiful detective work in relating 18 cases of gastroenteritis in patients in 4 states in the Upper Midwest to a dairy farm in South Dakota where there was diarrhea and death among those animals, caused by the same organism that infected the patients. The totally unproven part of the outbreak reported concerns the exact means by which the germ, Salmonella newport, was transmitted from the infected dairy animals to the patients. The article suggests that hamburger meat from beef produced in a "feeder lot" next to the farm was the source, but no organisms were isolated from beef, other animals, manure or soil at the "feeder lot". The most straightforward situation to account for the events reported would be that one of the infected dairy animals, or possibly a steer from the same farm, that was also sick with gastroenteritis somehow got sold as beef, and was distributed through the network described. Adequate data to exclude this possibility are not discussed.(1)

Irrespective of the means by which the unusual Salmonella was distributed, the evidence points to the dairy farm as the source. Paradoxically, antibiotics are not added to the feed used for milk-producing dairy cows. Antibiotics, we are told, were used for treating some, if not all of the sick dairy animals. Thus, if there was any selective pressure here it appears to be the use of antibiotics in high dose for therapy, rather than in the low doses used in animal feeds for growth promotion purposes.

There has been much speculation, but little incontrovertible data showing that resistant bacteria in farm animals are an important source of antibiotic resistant organisms in humans, with the very important exception of Salmonella. It has been shown that most bacteria that colonize the intestinal tract of animals are unlikely to survive very long in humans. Salmonellae are the exception; a large fraction of human infection due to Salmonellae (other than S. typhi, the .
organism that causes typhoid fever) come from animal sources (2). The problem of Salmonella infections in man is usually related to heavy contamination of foods of animal origin with Salmonellae from the intestinal tract of those animals. Occasionally there is person to person spread of Salmonellae; in the study by Holmberg et al (1) it appears that 3 of the 18 cases were infected, not by the speculated meat source, but either by other patients or a medical instrument (a sigmoidoscope). Thus, resitant Salmonellae are the most sensitive indicaters of the introduction of resistant organisms from animal to man.

In Britain, where the use of antibiotics in animal feeds was eliminated in 1971, there has been no dramatic change in the incidence of resistant bacteria in farm animals (3,4,5,6). See Tables I and II. The basis for the failure of such restrictions
to solve the problem appears
to have two facets: 1) antibiotics continue to be used in high doses to treat sick animals, and 2) various problems of spread of resistant organisms from animal to animal during rearing and shipping of the animals continued.

Although the experience in Britain is well documented over more than 10 years, a different view of the effect of restriction of the use of antibiotics in animal feeds was reported from the
Netherlands where a decrease in resistance was reported (7); see Fig. 2. Linton points out that this apparent decrease

in resistance was due to a single phage type of S. typhimurium, and pertained only to tetracycline resistance (see Fig. 2).

All students of the problem of antibiotic resistance agree that the presence of antibiotics in any environment, whether it be a laboratory dish, farm animals, or in a hospital environment, exert a selective effect favoring the resistant organisms. Thus, ideally, to decrease the prevelance of resistant organisms in the environment, and as a threat to human health, it would be prudent to decrease the use of antibiotics whenever feasible.

However, at this time there is no substantial evidence from any source to clearly show that antibiotics in animal feeds, as used in this country, pose a health hazard to humans. It is this dual use of antibiotics on farms, for the treatment of sick animals as well as for growth promotion that makes it difficult to identify which factor is more important in preserving or creating a reservoir of antibiotic resistant bacteria in farm animals.

Two additional points that must be considered are 1) that during the the 12 years 1971 to 1982, inclusive, there has been no significant increase in antibiotic resistance of gram negative organisms (frequently found in the intestine of animals and man) isolated from patients in American hospitals (8), in spite of the use of antibiotics in animal feeds, and 2) during this time there has been an increase in antibiotic resistance of a germ called Staphylococcus epidermidis, which has never been implicated as being obtained from animal sources. Most students of the problem think that resistance of that organism to antibiiotics stems from the use of antibiotics in humans. See Fig. 3..

The preceding discussion has dealt manly with the spread of resistant organisms and the impact of antibiotics in the environment on that phenomenon, but two aspects about Salmonella infections deserve comment here. First, it is extraordinary that so few cases came from such a large amount of contaminated beef(70,000 lbs.), and secondly, the disease described was especially virulent, suggesting

there had been recent "animal passage". It has been well established since the time of Pasteur that passing germs through living animals makes them more virulent (it is not yet known exactly how this occurs) and passing them in artificial laboratory medium makes the germs less virulent, or attenuated. In addition, with the exception ofthe Salmonella that causes typhoid fever, it takes very large numbers of organisms to infect an otherwise healthy animal. These facts, in addition to the circumstances described make the speculation more attractive that an infected animal, with lots of Salmonella newpport organisms in its tissues (as in the infected calf that died on the dairy farm described in the report [1]) somehow got into the beef production network and was eventually consumed by the patients, as well as by many others who did not get sick.

The problem of Salmonella infection of humans is largely a matter of humans eating food of animal origin that is contaminated with feces of animals carrying the Salmonella, usually without any disease at all in the animals. Although the animals themselves may also develop disease, or even death due to these organisms, it is the exceptional case where diseased animals find their way into human food. Even when this happens, even with relatively heavy contamination there is usually no disease because the organisms are easily killed by the usual heat of cooking.

Salmonella have been causing disease and death in humans and animals since long before the antibiotic era. The "traditional" methods of control relate to this basic problem of keeping animals healthy and avoiding the contamination of animal products destined for human consumption.

There is no question that the issue of antibiotic resistant bacteria remains an important problem. Work in the pharmaceutical industry continues at an active pace to produce new drugs that will be active against resistant organisms. And work continues in academic and other research centers to better understand the biochemical and genetic basis of reistance, to provide a basis for doing something about it. This effort should receive more substantial support from the National Instiutes of Health and other government agencies. Efforts are also being made in both human and veterinary medical circles to better understand the epidemiology and devise better methods to control the persistance and spread of of resistant organisms. These efforts also deserve support.

There are two special points about antibiotic resistance in Salmonella. The first is that most cases of Salmonella gastroenteritis do not require antibiotics for treatment! The disease is usually easily taken care of by simple supportive measures, such as replacing fluids. There are even observations that giving antibiotics to patients with Salmonella gastroenteritis may prolong the disease, or at least the excretion of Salmonella. The second point concerns the persistance of resistant organisms in the environment. Although much attention has been given to the fact that genes determining antibiotic resistance may be passed from resistant organisms to sensitive ones (i.e. "infectious drug resistance") the facts are that in most instances there is also some spontaneous loss of the resistant genes, converting the resistant organisms back to the sensitive state. This is surely one of the reasons that we are not surrounded by organisms, ever-increasing in the proportion that are resistant to one antibiotic, or more than one.

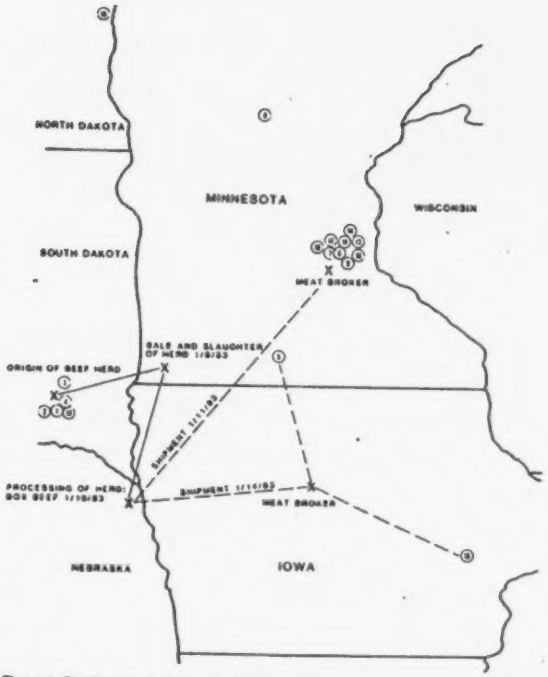

Figure 1. Distribution of 18 Cases of Resistant *Salmonella newport* Infection (Circled Numerals) in Relation to Origin and Shipment of Infected Beef, December 1982 through June 1983.
Broken lines denote suspected routes of shipment.

Fig. 1

(From Ref. 1)

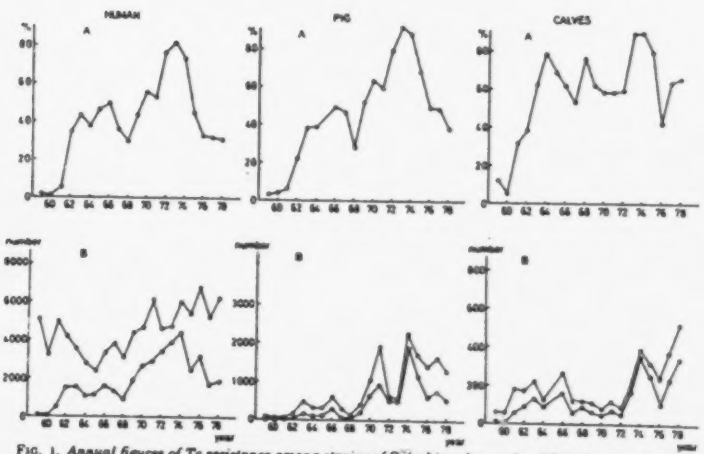

FIG. 1. *Annual figures of Tc resistance among strains of S. typhimurium isolated from humans, pigs, and cattle from 1959 to 1978. (A) Percentage of S. typhimurium isolates resistant to Tc. (B) Number of isolates investigated (●); number of Tc-resistant isolates (○).*

Fig. 2

(From Ref. 7)

Fig. 3 (from Ref. 8)

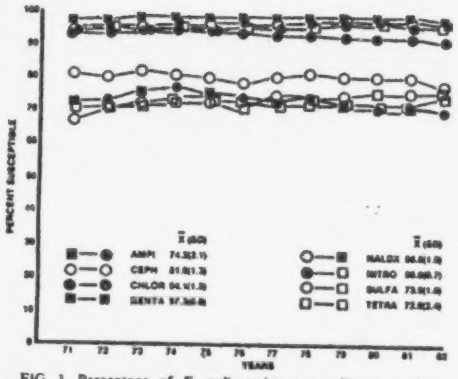

FIG. 1. Percentage of *E. coli* strains susceptible to various antibiotics. Abbreviations: AMPI, ampicillin; CEPH, cephalothin; CHLOR, chloramphenicol; GENTA, gentamicin; NALDX, nalidixic acid; NITRO, nitrofurantoin; SULFA, sulfonamides; TETRA, tetracycline; $\bar{x}$, mean; SD, standard deviation.

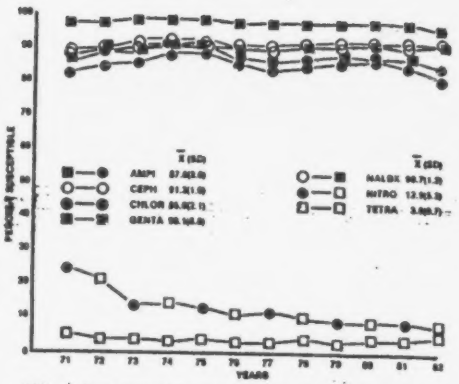

FIG. 3. Percentage of *P. mirabilis* strains susceptible to various antibiotics. For abbreviations, see the legend to Fig. 1.

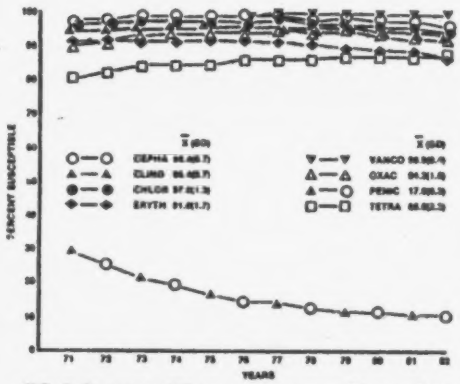

FIG. 2. Percentage of *S. aureus* strains susceptible to various antibiotics. Abbreviations: CEPHA, cephalothin; CLIND, clindamycin; CHLOR, chloramphenicol; ERYTH, erythromycin; VANCO, vancomycin; OXAC, oxacillin; PENIC, penicillin; TETRA, tetracycline; $\bar{x}$, mean; SD, standard deviation.

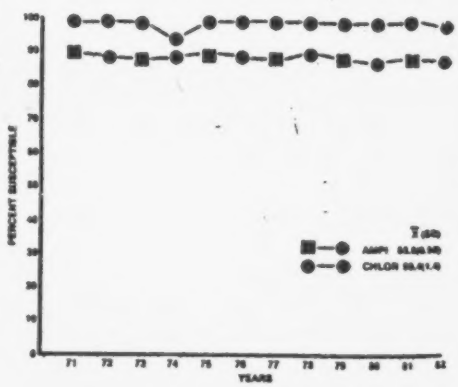

FIG. 4. Percentage of *H. influenzae* strains susceptible to various antibiotics. Abbreviations: AMPI, ampicillin; CHLOR, chloramphenicol; $\bar{x}$, mean; SD, standard deviation.

Tables I and II (frrom Ref. 5, labeled I and III below, as in work cited)

TABLE I.

The percentage of all salmonella isolates, submitted to the Central Veterinary Laboratory, resistant to individual drugs (after Sojka and Wray, 1980).

	Su	S	T	C	N	A	F	Trm
1971	55	81	1	<1	<1	4	2	0
1972	39	91	3	1	4	1	<1	0
1973	66	76	5	<1	1	<1	1	0
1974	64	48	5	<1	1	<1	<1	0
1975	77	39	3	<1	1	<1	1	<1
1976	75	65	5	<1	1	1	1	<1
1977	49	46	9	6	1	1	1	<1
1978	66	54	18	12	6	7	1	1
1979	56	54	16	11	7	8	2	5

Su, sulphonamide (50 μg); S, streptomycin (10 μg); T, tetracycline (10 μg); C, chloramphenicol (10 μg); N, neomycin (10 μg); A, ampicillin (10 μg); F, furazolidone (15 μg); Trm, trimethoprim sulphamethoxazole (25 μg). (Data 1"„ and above rounded up to the nearest "„).

TABLE III.

Percentage of *Salmonella* isolates from animals and their environment resistant to five important antibacterials (after Sojka and Wray, personal communications).

	Tet			Chlor			Neo			Amp			Trm			No. tested			Total
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	
1971	3	<1	1	<1	<1	0	1	<1	0	5	3	2	0	0	0	618	1201	433	2252
1972	3	<1	6	3	0	<1	9	<1	<1	<1	0	<1	0	0	0	945	643	528	2116
1973	6	<1	7	<1	0	<1	3	0	<1	1	0	<1	0	0	0	1262	564	1392	3218
1974	8	<1	3	<1	0	<1	2	0	<1	2	0	<1	0	0	0	1116	464	1107	2687
1975	5	<1	2	<1	<1	<1	2	<1	<1	1	0	<1	<1	0	<1	1483	381	1951	3815
1976	7	<1	4	1	0	<1	2	0	<1	1	1	1	1	<1	<1	2126	344	2255	4725
1977	23	2	3	16	1	1	2	1	1	2	<1	1	<1	<1	<1	1119	384	2326	3829
1978	38	2	4	28	2	1	14	1	<1	14	2	2	3	0	<1	1775	640	1971	4386
1979	35	5	3	24	5	<1	16	<1	<1	17	5	<1	11	<1	1	1825	771	1977	4573

A, *S. typhimurium*; B, *S. dublin*; C, other serotypes.
Data 1"„ and above rounded up to the nearest whole number. Tet, tetracycline; Chlor, chloramphenicol; Neo, neomycin; Amp, ampicillin; Trm, trimethoprim.

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Mr. GORE. Thank you very much.

One question just for starters, Dr. Sabath, your assumptions—your—your statements about the ineffectiveness of the British ban on subtherapeutic doses assumes that that ban has been enforced in a way that really accomplishes the goal that its authors sought, and is there not substantial evidence that it really hasn't been effective because there's been a dramatic increase in prescription of antibiotics by local veterinarians and that essentially the same practices of feeding subtherapeutic doses for growth promotion have continued unabated in England?

Dr. SABATH. I, obviously, not being a farmer in Britain, don't have firsthand information about how strictly that's been enforced. I've heard rumors—and I don't know if it's a fact—that the use, actually in high levels for therapy, has increased, and I think it's related to the point I tried to summarize, that there are four major influences in our environment selecting resistant organisms: Namely use—those two uses in man and the two uses in animals, and as I quoted from Linton in this marvelous little book dealing with resistant bacteria, that attention to only one will probably have no effect whatsoever, and I think—I personally think that's what the British example shows, that antibiotics continue to be used for therapy—possibly even in higher levels, although I don't have data to that effect.

The editorial—I didn't comment on it, nor did I list it in my bibliography, but in the same issue of the New England Journal of Medicine in which the article by Holmberg and Cohen and others appeared, suggested that there is wisdom in the Swann committee's suggestion. I'd like to call attention to this little book which is—in which that item five in my bibliography appears, which is from a meeting held in London in 1981, in which a number of prominent scientists and veterinarians dealt with that issue.

The recommendation of the Swann committee was held with—and actually laughed at there—as being grossly ineffective. The editorial in the New England Journal's written as though the experience from Britian was not available to us. We already know what happens when one bans the use there from that British experience, and this book here really sums up a lot of the aspects about that.

Mr. GORE. I want to ask you, Dr. Cohen, to respond to some of the criticisms that you've heard, but before you do so, do you have anything to say on this about the British experiment? Is there any evidence that the—that the practices of feeding subtherapeutic doses have—have continued?

Dr. COHEN. I've not seen anything formal about it. I've heard similar rumors to the effect that the ban has not been effective in the sense that the agents are still used. It's not clear to me whether they're used in subtherapeutic or therapeutic doses, but I think that that's been a concern of public health people in England, that the efficacy of the ban is not as high as they would like.

One other aspect about the change in resistance and such in England, Dr. Rowe has some very impressive data looking at Salmonella resistance following the introduction of a drug which has been relatively important, a new drug in human medicine which is trimethoprim, which was also introduced for animal use, and beginning at about 1971 to the present time, there's been a tremen-

dous emergence of a particular organism that has trimethoprim resistance, and he's postulated that this is related to antimicrobial use, whether it's subtherapeutic or therapeutic in animals.

Mr. GORE. Let me ask you to respond to some of the criticisms that Dr. Hays and Dr. Sabath have leveled at your study, and Dr. O'Brien, you're welcome to jump into this when you feel the urge. First of all, the criticism was stated that—that the specific plasmid was not found in the—on the farm in question, but just on a—on a farm next door, and it wasn't recovered from the beef in question, either, the bacterium, either from the beef feedlot or from any samples of hamburger.

How serious a weakness do you think that is in your study?

Dr. COHEN. Well, I think the epidemiologic evidence identifies the beef herd as the source of infection. It would have—there was no possible way to obtain specimens from the beef, although there might have been some specimens still frozen in people's refrigerator when we conducted the initial investigation in Minnesota. By the time we came to suspect the beef, it was all eaten.

Mr. GORE. Yeah.

Dr. COHEN. So there's no way to go back in these kinds of retrospective studies and get specimens. I suppose we could have attempted to isolate the organism on the farm. All the herd had been slaughtered so there were no animals present. If we had isolated it there, then I'm not sure that the criticisms would have been any different as to how it got to that particular area.

I think, again, we go back to the preponderance of epidemiologic evidence in this case——

Mr. GORE. Yeah.

Dr. COHEN [continuing]. Which draws together the distribution of the meat product with this organism, to say that at some point in time, whether it got into the dairy herd from the beef herd or got into the beef herd from the dairy herd isn't clear, but that at some point in time, it was in the beef herd. In addition, we know that the farm families who were infected had acquired their beef 2 to 3 months, at least, before the meat was distributed in Minnesota-St. Paul, so there's evidence that this organism persisted in this herd, again for a several months period of time.

Mr. GORE. Yeah, and then you did find it in a calf on the neighboring farm.

Dr. COHEN. Well, that was—that was a pathologic specimen that had been obtained in 1982 and stocked——

Mr. GORE. Yeah.

Dr. COHEN [continuing]. Stored specimen.

Mr. GORE. Yeah. Well, Dr. Sabath and Dr. Hays—did you want to add something to that?

Dr. O'BRIEN. Just one aspect of it that might be worth mentioning is that while the excellent detailed epidemiology is important and makes the possibility—or in this case, very high probability of a trail very tangible and easier to follow, still the fact remains that it isn't that difficult to find animal isolates and human isolates that have very closely genealogically linked plasmids carrying the—I think the clearcut message that the pools, the resistance plasmid pools of the two populations are interconnected.

And if they are, for purposes of the issues here, it may not make that much difference. It's nice to have examples and it reinforces the point, but even if they weren't connected by food—food products, by a chain of beef animals and so on; if they blew to the consumers in the prevailing winds, the issue would still be there in terms of the significance of antibiotic resistance in animals and in humans.

Mr. GORE. Well, there's no doubt in your mind, Dr. O'Brien, as the originator of this identifying technique, that the bacteria was—or that the plasmid was the same in—in the animals as——

Dr. O'BRIEN. That's correct.

Mr. GORE [continuing]. In humans that were infected.

Dr. O'BRIEN. Yes.

Mr. GORE. Well, Dr. Hays and Dr. Sabath, isn't the epidemiological evidence just overwhelming in this case? I mean, isn't it almost impossible to avoid the conclusion that this came from the—from the beef in question?

Dr. SABATH. Well, I think that—I'd say it's very easy to question. There's absolutely zero substantiable evidence that it was ever in the beef at all.

Mr. GORE. What about the fact that—what about the epidemiological evidence that all of the people that got sick ate the same beef from the same place?

Dr. SABATH. Well, one, that's not true. The suggestion is that 15 of the 18 ate the beef and three, it's suggested from the epidemiologic evidence that it was acquired either from a sigmoidoscope in one case——

Mr. GORE. Yeah.

Dr. SABATH [continuing]. Or from other people in the household is suggested in the other, so the report, as one reads it, suggested three of the 18 never ate the implicated beef at all. So we know three cases had nothing to do with it.

Mr. GORE. Yeah.

Dr. SABATH. Nothing directly, but they got it from other instruments or people.

Mr. GORE. Let me ask Dr. Cohen to respond to that.

Dr. COHEN. I think that this is the difficulty we talked about before in transmission, that if you look to where those people acquired their infection, it was from an individual who had consumed the product, so the ultimate source is the animal reservoir, despite the fact that there might have been in an individual case person-to-person transmission or person-to-sigmoidoscope-to-person.

Mr. GORE. So, the—now, the three people who didn't consume the beef, two of them were related to people who did consume the beef?

Dr. COHEN. Yes, that's correct.

Mr. GORE. And the—and the third one was the person with the sigmoidoscope, is that——

Dr. COHEN. Yes.

Mr. GORE. And he was an unrelated—Dr. Sabath?

Dr. SABATH. If I could come back, although it may seem like there is some difference of opinion between us here, I don't think——

Mr. GORE. It does seem that way. [Laughter.]

Dr. SABATH. I'd like to, if I could, resolve it, because I think the basic facts, if we stick to the facts, are very clear and it really incorporates everything that's been said here. In fact, I think a failure to focus on those facts has grossly muddled the issue before this committee and so I'm really honored to have the chance to be here, especially with these gentlemen.

I think the beautiful——

Mr. GORE. You talk the same way we do up here sometimes. [Laughter.]

Dr. SABATH. Well, I think these really all fit together because the uniqueness of the organism found in these patients and on that dairy farm, I think very clearly showed—and I think we'd all agree—that it was the same germ in those patients as on that dairy farm. Isn't that—there's no question—I don't think anybody's going—here is going to question that.

Mr. GORE. Dr. Hays, do you agree with that, too?

Dr. HAYS. I agree with that.

Dr. SABATH. So that's absolutely clear. Now, I brought up the evidence just as pure common sense. I mean, it'd be—there's absolutely zero direct evidence that organism was ever in the beef, but that's a relatively minor point, but——

Mr. GORE. Isn't there overwhelming circumstantial evidence?

Dr. SABATH. Not at all, not at all, because—I don't think it's overwhelming, and for another——

Mr. GORE. Wait a minute, now wait a minute. Eighteen people got sick.

Dr. SABATH. Yeah.

Mr. GORE. Fifteen of them ate beef from the same place.

Dr. SABATH. That came from a pool of 40,000 pounds of beef, we're told.

Mr. GORE. Fifteen of them ate beef from a pool of beef that had beef from the farm in question. Two—two others were family members of people who had eaten beef from that pool in question, and the final one was a special case that they have accounted for through another—through another means, which is also documented.

Now that circumstantial evidence is—is pretty strong, it seems to me. Why——

Dr. SABATH. Well——

Mr. GORE. Why isn't that strong to you?

Dr. SABATH. Well, it's not strong at all to me and I—because you have to get down to the basic biology of the organism. The related points—if I'm not mistaken, 2 of those 18 actually lived on the dairy farm where there was this epidemic of disease among the farm animals. Isn't that right, Dr. Cohen?

Dr. COHEN. I believe that only one——

Dr. SABATH. One actually lived on the farm. The second point is that the number—considering the enormous amount of beef, there are only 18 cases and only 15 allegedly from eating the beef. Now, when you stop to think how many servings of beef could come from 40,000—that's a huge number. If it really is widespread in that beef, which it may or not be, how come there aren't more cases?

A second issue about this which is terribly important and wasn't mentioned at all in the article is that disease, Salmonella gastroen-

teritis, in man is usually a relatively benign illness. This was a very serious illness and about half of them had to be hospitalized for some time, so it's extremely unusual for human beings to be that sick with Salmonella gastroenteritis. What's different about that?

Now, I'll tell you what's different about it right now. One of the fundamental issues of pathogenicity of organisms—it's clearly known since the time of Pasteur—is that one way germs become more virulent—if you pass them in one animal, then another, and then another in rapid succession, that enhances virulence.

That would suggest that the organism infecting those people came directly from an infected source, such as an infected animal possibly involved in the epidemic of Salmonella infection on the dairy farm. Now, I'm not saying that one—that farmer sold—had a beef steer that was somehow sold to that meat processing plant and that made its way into the beef, but that would be the simplest explanation.

A second one would be—and actually, I talked to Dr. Osterholm, who is the second author in that article who just works a few blocks down the street, long before I knew I was going to be coming here. I said, "What about this? How did this happen?" He said, "Well, we know there were breaks in the fence and those cattle were intermingling." And I'm sure—I mean, I believe everything that's written there. It's the interpretation that I take issue with.

Even if that's how it was transmitted, and it's possible, then one would have to focus on keeping sick animals from nonsick animals, but the key and basic point, and Dr. Hays really focused on that, and the article just totally ignores it, the basic point is if, in fact, those germs somehow got introduced into that—where these beef were being fattened up with eating feed laced with subtherapeutic levels of antibiotic, the fact that it's tetracycline that's laced in the—in the feed for the beef animals would not be of any selective advantage at all with that organism because it was already resistant to tetracycline. It would have not been, in that particular setup that that would not have made much difference because the other organisms would also be tetracycline-resistant, as Dr. Hays showed from his solid data.

So the selective pressure is probably on the dairy farm. Somehow it got there; I don't think there's any question; I just say there's no proof that it was in the beef. It could have been on the hands of somebody else or in that infected single animal.

Mr. GORE. Dr. Hays.

Dr. HAYS. Might I relate to it if, assuming that these were finished cattle, 59 head would probably yield about 6,000 pounds of hamburger meat, so that 40,000 pounds of hamburger probably came from about 6,000 pounds from that beef farm and 34,000 from some other sources. There could have been a sick animal along the way. Now, if one was a heavy carrier of Salmonella and coming to the slaughter plant ill, this should have been caught in the antemortem inspection and the postmortem inspection, but it could slip through that way. But, see, there's obviously a great deal of dilution. Of that particular herd, only about half—46 of the animals also went to another processing plant and we have no evidence that those 46 from the other—so it wasn't a widespread—we should

have had similar outbreaks from the 46 others that went to another plant and went through another distribution system. We have no evidence that that was the case.

But even if we assume that the beef in the Minneapolis area did contain Salmonella and brought about this infection, that still doesn't mean that the use of tetracycline at a subtherapeutic level had any influence on the development of the resistance or the selection for that resistance. If they were using tetracycline with any regularity on that beef farm, and the report suggests that he was using it throughout the period in those animals all through this process, the change in their resistance pattern would come within the first few weeks.

The tetracycline-resistant organisms would have survived; they would have been the predominant organisms. So another tetracycline-resistant organism coming in would not have any particular advantage because of its tetracycline resistance.

Mr. GORE. Let me ask Dr. Cohen and Dr. O'Brien to respond.

Dr. COHEN. Well, I think there are several points. In one instance, the questions about the actual effect in the herd itself are unanswerable. We're talking about trying to impose a prospective study which is going to first determine what the frequency of tetracycline resistance is in the herd; then supply antimicrobials; then infect with an organism. I mean, we had no data. What we have is a retrospective analysis of events that transpired and what we know also is, there are data which have been developed by the FDA and others which show that if you take and infect an organism—in this instance, an animal—with a resistant organism and feed them subtherapeutic doses of antimicrobials, that this prolongs the excretion and the persistence of the organism.

So that I think that there is evidence to support the hypothesis. What we're being asked to do is, to some extent, comment on things that are far beyond our control to determine.

Now, there—I think there was one other point that was raised that I didn't have a chance to really address about other sources for transmission. The milk which was produced from this dairy herd was sent to a large producer and pasteurized. Its distribution—and I think a large part of it was made, perhaps, into cheese—so there's no evidence that this could have been the source based on food histories from individuals.

Raw milk was consumed by the one owner of the farm, but not any of the other individuals who lived on separate farms, so that's not a potential source.

The only information we have about whether or not there were any animals from the dairy herd which were sold to slaughter is from the two farmers who deny it and only report the 105, you know, head that they had in the beef herd.

Dr. SABATH. Did they have this—I wanted to call Mike yesterday before coming here to find out—that on that farm where they had the dairy animals, do they also have some beef animals or not?

Dr. COHEN. I don't know. My impression is that they do not; however, Mike wouldn't know that. It would be the State epidemiologist in South Dakota who would have that information.

Dr. SABATH. Because I——

Mr. GORE. Go ahead.

Dr. SABATH. If I just may comment. Obviously I'm a physician taking care of human beings and studying bacterial resistance in the laboratory, but on the radio in Minnesota last week, I heard a farmer interviewed suggesting that high power lines influence the milk production of his dairy cattle, suggesting he wanted some sort of compensation from the power company, and he said that the influence was so bad that his cows were producing less milk and he had to sell them for beef, and so I just wondered—I don't know if that was just——

Mr. GORE. They've interviewed the two farmers involved and they said they didn't sell any of their dairy cattle for beef.

Dr. SABATH. Well, the question is: Do they also have some beef cattle on the same farm? That's what I don't know the answer to.

Dr. O'BRIEN. Again, I would think that, important as the outbreak is as an illustration and one that we probably need more of and could get more of, that focusing too much on that and the details of that may distract us from the main issue, which is populations of bacteria, that animals and humans are just houses—housing for large populations, large complicated populations of bacteria and that in essence, the antibiotic resistance system develops in those populations as some function of how antibiotics are used.

As more antibiotics are used, more antibiotic resistance genes ultimately emerge. Initially, before there were antibiotics, there were hardly any known, from retrospective studies, and new ones keep appearing so that the evolutionary pressure to come up with new antibiotic resistance genes comes from application of antibiotics to large complicated populations of bacteria.

It also—the use of antibiotics also promotes the possibilities of those genes ultimately getting onto plasmids where they'll be more mobile between species——

Mr. GORE. Yeah.

Dr. O'BRIEN [continuing]. And probably—although this is something that isn't—we only have glimpses of yet—probably plasmids differ in their efficiency to colonize, to move, to persist between episodes of antibiotic usage is the sort of thing that Dr. Hays is seeing an illustration of, and more antibiotic usage probably promotes evolution of better plasmids. I think these are all things that we could more or less agree upon in principle in bacterial populations.

And I think the evidence that we've been able to put together from what we did, from what Dr. Cohen has, is that these—the overriding issue is that these populations in the animals and in the humans are connected. And, again, I don't think that—whether they're by air or whether the bacteria were mailed between them—wouldn't make that much difference if the populations exist as——

Mr. GORE. Yeah.

Dr. O'BRIEN [continuing]. Genetic recombination laboratories to get more plasmids, more resistance genes. Then they will have an influence and the amount of that influence, I think, is the issue, but not necessarily the details of any particular episode of transmission.

Mr. GORE. Let me ask just a couple more questions before turning to my colleague.

Do all four witnesses agree that—that the—the bacteria—that the bacteria and the plasmids in livestock are often the same as that found in human beings?

Dr. SABATH. Well, I think we'd all agree—and Dr. O'Brien has beautifully shown that the resistance genes are essentially the same.

Mr. GORE. All right.

Dr. SABATH. They're actually only a handful to deal with of those have—a relatively small number, but they are the same. The bacteria themselves are often fairly different and that's why one of the key things about Salmonella—they may be exactly the same, but it's been shown by many people working in veterinary medicine that it's very hard to get the bacteria of animals to survive very long in man, but Salmonella is one of the exceptions.

Mr. GORE. Well, let me be more precise, then. The resistance genes can—do exist, both in the bacteria populations in animal herds and in people; right?

No disagreement there. All right.

Second fact, that—perhaps you can all agree on—the—the broader the use of antibiotics, the greater is the evolutionary pressure for the development of resistance genes by the bacteria populations, both in—in animals and in humans. Is there agreement on that?

Dr. Hays, we lost you on that one?

Dr. HAYS. I would agree up to a point, and my disagreement in all of this is—comes about, say, thinking of the proposed actions that—or the actions that have been proposed——

Mr. GORE. Now, we haven't gotten there yet.

Dr. HAYS. Let me go on here for just one point. I think that there's real good reasons why you have to use more therapeutic—if you pull away the subtherapeutic——

Mr. GORE. Yeah.

Dr. HAYS [continuing]. And one of those is that the alternatives—we have no real good alternatives for the gram-negative bacteria, so I would expect the therapeutic use would have to increase—our data would show that if we pulled away, so that in the end, the total exposure, or the total antibiotic pressure might not change all that much.

And Dr. Cohen is right in that our data would suggest that antibiotic pressure or the use of antibiotics would extend the excretion of Salmonella. There are also data that show that it has no effect, so it's a balanced thing and——

Mr. GORE. Well——

Dr. HAYS [continuing]. Some of our own data would support that.

Mr. GORE. OK, but without jumping ahead to—to the proposed solutions for this, you agree that the more antibiotics are used, the more development of gene—of resistance genes will occur in bacteria. OK, both in animals and humans.

Now, the—the amount of antibiotics being used in livestock now is—is quite large. Someone told me it was over 50 percent of all the antibiotics used in—in the country are used in livestock. Is that—is that correct? Anybody confirm or deny that? Forty percent?

Dr. HAYS. We can get very misleading information by just looking at the total pool of antibiotic usage and relating the percent-

age. For example, the major—so many have suggested that there's been a major increase in antibiotic usage in animals in the 1970's. That's primarily brought about by the fact that the ionophore drugs have been—are now being included in the total picture of antibiotic usage. They were not in that picture prior to the 1970's——

Mr. GORE. I'm not measuring increase from decade to decade.

Dr. HAYS. Well—but see, that's a big part of that 50 percent and they're widely used as coccidiostats and widely used as rumen regulators in beef cattle production, but they're a completely different class, different class of antibiotics.

Mr. GORE. But they are antibiotics.

Dr. HAYS. They are antibiotics.

Mr. GORE. And if they are included, then, 50 percent or more of the total antibiotics used are used in—in livestock?

Dr. HAYS. My estimates would be about 45 percent.

Mr. GORE. Forty-five percent. All right. I'll come back to it, but I want to recognize my colleague, a member of the subcommittee, Mr. Volkmer.

Mr. VOLKMER. Thank you, Mr. Chairman. I appreciate the opportunity to be here to go over this with you. I have some problems, not only with the Center for Disease Control study, as Dr. Sabath has said, to some degree, if we want to be accurate, completely accurate in what we're doing, and the—Dr. Sabath has addressed that, and I'd like to know, Dr. Cohen and Dr. O'Brien, how do you explain that out of all of that meat that was eaten—if the beef was the contaminating factor—that not more than 18 cases totally were reported? How do we explain that?

Dr. COHEN. Well, we know from previous investigations of the salmonellosis that here we're dealing with reported cases. For an isolate to be reported, an individual: (1) Becomes sick; (2) goes to physician; (3) he gets a culture; (4) the culture goes to a laboratory; (5) it's serotyped; (6) it goes to the State health department and gets reported to us. So there's a very—a very long chain.

Now, we conducted a series of investigations in the 1960's and 1970's and we found that when we went out into the community and actually did a survey to find out how many people were sick versus how many isolates were reported, that we were getting about 1 percent of the reported isolates—of actually occurring disease, so we estimate that when we find 1 case reported, that there's probably been 100 cases.

Now, there may be some biases so the more serious cases are those that are reported, but—of patients who experienced clinical diarrhea, so if that holds for this instance—and there's no reason to suspect that it wouldn't—we're talking about maybe 1,800 individuals who would have had symptomatic diarrhea. So I think that—you know, that opportunity there is for a reporting artifact represented being so small.

In addition, we have a—a population that has had a specific selective pressure applied to it. It may well be that antibiotic usage is one of the reasons why these patients experience severe disease or manifest the disease at all, so we may not be only speaking about individuals who were infected or colonized—let's say that an individual who ate the infected material didn't become ill. These individuals may have been in that category if they hadn't taken anti-

microbials, so there may be an additional factor here why we only detected the small number of individuals.

Dr. O'BRIEN. One other point I'd like to make is the paradox that the Salmonella are two things in terms of their use. They're excellent for epidemiological tracers because they are—they are probably the one strain of bacteria that we can serotype, that there's a system in place to find. So that they get our attention because they're the ones that we can find and can trace and get out and look at plasmids in.

But they represent—as tracers, they represent paradoxically a tiny fraction of the bacterial populations of animals or of humans, just the conspicuous ones. So I think they're interesting. If you can find pathways or if you can find interchange in Salmonella, then presumably these—for all we know—these same pathways are available for the 10-fold, probably 100-fold, 1,000-fold greater numbers of other kinds of bacteria in animals and in humans that have resistance genes and plasmids can move through the same pathways, but which we don't have a handle on tracing.

So I think you keep in mind that the Salmonella, are conspicuous as tracers for the problem—and excellent ones—but probably vastly—certainly vastly underestimate the volume of resistant bacteria in these—in the populations of both. Is that——

Dr. COHEN. I agree. I think one—one further point about susceptibility of the host, I think, is important. If you have a common-source outbreak, say a banquet, in which you know you have a contaminated food product and you have 100 people eat it, you may only have 25 people who become ill. There are a variety of factors which determine whether an individual who has consumed a contaminated product becomes ill. And so I think this comes into play as well.

Mr. VOLKMER. All right, then. We've had Salmonella long before we had these—or used the therapeutic use of antibiotics; have we not? I suppose as long as man's been eating meat? Is that correct?

Dr. COHEN. Oh, yes, Salmonella were described in the late part of the 19th century by Salmon.

Mr. VOLKMER. Right, and if we—let's say assume that—that we no longer used antibiotics for subtherapeutic use, as has been described by Dr. Hays, is it your position that we would have less outbreaks of Salmonella?

Dr. COHEN. There were—there were questions that—that is a question that has been raised before. There were some concerns that the use of the agents by increasing the persistence of resistant Salmonella causes a greater spread among animals so therefore, you're dealing with more—more infected products and potentially more people who can be infected.

I do not really have that much familiarity with that literature, you know, to comment on those data. Linton, who has been referred to before, has some interesting data which suggests that the environments in which the animals are raised are very important for the perpetuation of resistance, so I think any study that we consider has to remember that these animals have intimate contact with their environment so that even if you withdraw agents, if there are resistant organisms in the environment, they may persist for some period of time.

I think it's difficult to account for what the effect would be on the basis of a withdrawal.

Mr. VOLKMER. But like Dr. Hays has said, even if you have, then—if you're not using the subtherapeutic antibiotics and you have any outbreak of any type of disease within the animals, you're going to have therapeutic use. Is that correct? If we don't have therapeutic use, we're going to do away with a lot of animals eventually, aren't we? If we have antibiotics for subtherapeutic or therapeutic use?

Dr. COHEN. I think that when you have a disease, you'll be inclined to treat it with an available and appropriate drug.

Mr. VOLKMER. I mean, if you—but if you say that you cannot use it for subtherapeutic or therapeutic because of the resistance, then you're not—the animals usually are not going to be able to be used, are they, for meat?

Dr. COHEN. Well, I don't know. I think it's basically the FDA's decision as to what they propose to restrict. I think basically the concept here has dealt with subtherapeutic use. Restriction of therapeutic use, I think, is a different question.

Mr. VOLKMER. Oh. What's your comment in regard to Dr. Hays' statement that if you restrict the subtherapeutic use, that you'll have to have more therapeutic use, and therefore, you're still going to be using antibiotics?

Dr. COHEN. I don't—I don't know that that is the result.

Mr. VOLKMER. There are other diseases other than Salmonella that are transmittable from animals to humans; is that not correct?

Dr. COHEN. Uh-huh.

Mr. VOLKMER. Everybody agree on that? Are we concerned—are you concerned about any of those other diseases in the use of subtherapeutic drugs?

Dr. O'Brien, Dr. Cohen?

Dr. O'BRIEN. Yes, I think—yes, that was the point I was making. I think that we're—you're concerned with the whole—you're concerned basically in terms of the resistance problem with the resistance genes and the resistance plasmids and the kinds of bacteria that they happen to be in aren't, since they can move around so well, aren't really a big concern. They happen to—it happens to be very convenient to find them in Salmonella, so that I think the—what you'd be mostly concerned with in trying to evaluate this is the large populations of bacteria in animals that perhaps aren't causing a disease at all, aren't even pathogens, but which are almost innocent bystanders in the antibiotic wars, but who also have to protect themselves by developing antibiotic resistance genes and plasmids, and once they're protected and developed and in circulation, some of those will get into pathogens, and so that I think it's—the mobility of these is so great that the kinds of bacteria almost don't make any difference, except that, as I say, some are more easy to trace than others.

Mr. GORE. Would the gentleman yield——

Mr. VOLKMER. Yes.

Mr. GORE [continuing]. Briefly?

If I understand what you're saying correctly, your real concern is that heavy antibiotic use promotes the development of—of specific

genes that confer resistance to those antibiotics and even if the particular bacteria where that gene is developed is not a threat to humans, it is still a problem because genes can be transferred from one kind of bacteria to another through these plasmids that—that carry the gene from, say, a Salmonella bacteria to some completely different kind of bacteria, and when you have a population of bacteria that is constantly bombarded with antibiotics, the evolutionary pressure is very strong for the development of these resistance genes, which then have a—a likelihood of—of jumping to other kinds of bacteria and conferring on these other bacteria the resistance to the antibiotics that are being used, both in animals and in humans. Is that——

Dr. O'BRIEN. That's it, yes.

Mr. GORE. I thank my colleague for yielding.

Mr. VOLKMER. Yes. But not all those bacteria are necessarily harmful to humans.

Dr. O'BRIEN. Very few.

Mr. VOLKMER. Very few, correct. And how far—in other words, what studies can you cite to show that we have—in other words, a growth maybe in today's society of humans of the increased resistance in bacteria that are associated with animal bacteria? As a result of using the subtherapeutic antibiotics?

Dr. O'BRIEN. I think, well, the level—Dr. Cohen may say something about the Salmonella. He's done studies of Salmonella in humans generally when there may be some evidence. I think the level of evidence is that we do have—and Dr. Cohen—and Dr. Sabath presented some of this—that we do have in human populations a certain fairly constant level of antibiotic resistance now, at least for the last decade, at least in this country. In other countries, it's different, the last decade in which it's been looked at reasonably constant, within which there are some significant shifts, and I think that that's—we can say that some of—some of the plasmids—and I don't think you can yet give a quantitative figure and some of the resistance genes are—certainly some of the plasmids have their origin or are more prominent, likely to have arisen in animal populations.

But I don't think there's existing data except for knowing that these things probably exist, you can give quantitative figures as to—to the extent. I don't think we know that for the whole population at this point.

Dr. COHEN. I agree. I think that Salmonella has been most studied and we—we discussed that there is probably somewhere between a quarter and a third of Salmonella resistant to multiple antimicrobials. The phenomena that was discussed before, though, of genetic transfer has been postulated as having occurred perhaps in the case of the gonorrhea organism and the Hemophilus in that the genetic element, which is responsible for resistance, is closely related to the genetic element which comes from gram-negative organisms.

So that type of sharing of genetic material may have already occurred. So that there are—I don't think it's necessary to restrict our concerns about antibiotic resistance just to organisms that are directly related from animals.

Also, I think that we—we have to be careful that we don't concentrate primarily on animals and subtherapeutic use in animals; that antibiotic resistance results from both appropriate and inappropriate use in animals and man, so that it's—it's a very complex scheme in which there's influences from all sides and then the final result is that you get resistant organisms.

Frequently you can't actually trace the real—the origin of those strains, but in a few instances, I think you can.

Mr. VOLKMER. About how many total cases of Salmonella do we have here in the United States annually?

Dr. COHEN. Well, we have 40,000 isolates that are reported, and using our estimate again of reported-to-cases-which-are-unreported, we estimate about 4 million cases.

Mr. VOLKMER. And we don't—how far back can you go in the history of the country and—in reporting the numbers?

Dr. COHEN. Oh, well, we—the Center instituted a surveillance system in the early 1960's as a response to some problems with hospital outbreaks associated with powdered eggs and such and some of those types of products. Early on, there were less than 10,000 or so cases reported. The system really geared up to have consistent reporting, I would guess, in the early 1970's. We were getting in the 20,000 reports per year and it's been a steady increase over the last 10 to 15 years, beginning particularly in 1976.

Mr. VOLKMER. What do you mean, "particularly in 1976"?

Dr. COHEN. The curve was somewhat flat from about 1971 to 1976. We think that part of that flatness relates to actions that were taken regarding pet turtles which were a significant source of Salmonella in the United States. There was about, maybe a 19-percent reduction in childhood salmonellosis as a result of legislative action which—regulatory action which prohibited the sale of pet turtles.

And so an overall trend in the increase in salmonellosis might have been masked by that decrease, but about 1976, it picked up again and has been increasing almost on an annual basis.

Mr. VOLKMER. What percent on an annual basis?

Dr. COHEN. I'm not sure; I'd have to calculate.

Mr. VOLKMER. Appreciate if you'd supply it for the record so that we could have it.

Mr. GORE. We'll hold the record for that, and also, we're going to be looking at a lot of these questions in tomorrow's hearing on the human—the use of antibiotics in humans.

[The information follows:]

SALMONELLA RATES BY YEAR

YEAR	ESTIMATED POPULATION (in thous)	NUMBER OF SALMONELLA ISOLATES	PERCENT CHANGE	RATE PER 100,000	PERCENT RATE CHANGE
1970	203302	24304		11.955	
1971	206827	25561	5.17	12.359	3.38
1972	209284	26326	2.99	12.579	1.78
1973	211357	26634	1.17	12.601	.18
1974	213342	23902	-10.26	11.204	-11.09
1975	215465	23171	-3.06	10.754	-4.01
1976	217563	23174	.01	10.652	-.95
1977	219760	27071	16.82	12.318	15.65
1978	222095	28881	6.69	13.004	5.56
1979	224567	31770	10.00	14.147	8.79
1980	226546	29335	-7.66	12.949	-8.47
1981	229518	35704	21.71	15.556	20.14
1982	231786	37683	5.54	16.258	4.51
1983	233981	38881	3.18	16.617	2.21

Mr. VOLKMER. The other thing is I'd like to have that also in percentage of population growth in the country, too.

Dr. COHEN. Rate, yes.

Mr. VOLKMER. Yeah, the rate as against the rate. And the last question that I have, another thing that concerns me, out of the large number of total cases that you estimate that we've had here in the United States, approximately 4 million in a year, have you been able to make an epidemiological determination as to any of those the same as you did in the South Dakota/Minnesota case?

Dr. COHEN. An earlier study that we published earlier this year tried to look at some of the investigations that we conducted and there were some 52 investigations since about 1971, and I think the limitations on that analysis are many, but approximately—oh, 40 to 60 percent of outbreaks were associated with organisms of animal origin.

Mr. VOLKMER. Just for my personal use, I've always thought that if you cooked the meat thoroughly, you didn't have to worry about Salmonella. Is that correct or incorrect?

Dr. COHEN. Well, I think——

Mr. VOLKMER. Is that correct? One—Dr. Sabath says yes. Dr. Hays, yes. Dr. O'Brien?

Dr. O'BRIEN. If you cook adequately, yes.

Mr. VOLKMER. Yeah.

Dr. COHEN. I would hope that that would be very effective. I have to qualify it because I'm afraid what happens is that once an organism becomes introduced in a household—whether it be on a cutting board or some other kitchen surface—that it may persist there so that you cook the meat—you have no problem with the transmission from that source. However, that if a mother then prepares the baby's formula on the same surface and transmits it to the

child, that that doesn't help the secondary case. Since a large proportion of Salmonella cases occur in children less than one, we think that this is a tremendous source—that is cross-contamination, or person-to-person spread from organisms that are introduced into the household. We're concerned that—that consumer education may be of some help, but I think there are limitations.

Mr. VOLKMER. Does the Salmonella bacteria exist in man?

Dr. COHEN. There are species-specific organisms. For example, Salmonella typhi doesn't exist in animals. Gallinarum and pullorum are primarily species or strains that are poultry-oriented and so there are some that are very selective in which types of other organisms they'll infect.

Dr. O'BRIEN. And, of course, many that are equally adept at colonizing both.

Dr. COHEN. Yes.

Mr. VOLKMER. Oh, my point is—what I'm trying to say, can man transmit without contact with animal?

Dr. COHEN. Yes, typhoid.

Mr. VOLKMER. Other than typhoid?

Dr. COHEN. Well, again, the answer to that is yes, but we like to try to determine where that Salmonella came from——

Mr. VOLKMER. What I'm trying to——

Dr. COHEN [continuing]. The person that became infected with.

Mr. VOLKMER. What I'm—that's what I mean. In other words, there are certain viruses, et cetera, that man has, that man transmits. Salmonella bacteria, does man contain that within his organism so that he could transmit it even though—let's say I was a vegetarian. Never touched, never ate meat.

Dr. COHEN. Well, you could acquire it from another source that had been cross-contaminated from an animal reservoir and that's not an infrequent event.

Mr. VOLKMER. But I wouldn't be a—what do you call it, a source myself?

Dr. COHEN. A carrier?

Mr. VOLKMER. Carrier.

Dr. COHEN. The typhi is the best example of that. We don't know of animals which are the source of typhi. It's primarily humans, that humans spread it to other humans. But other serotypes are very adept at infecting both animals and man.

Mr. VOLKMER. Still not completely—maybe I don't know the terminology. Is typhi a Salmonella form of Salmonella—Salmonella?

Dr. COHEN. Yes, it causes typhoid fever.

Mr. VOLKMER. I know—I know that, but I didn't know it was a form of Salmonella.

Mr. GORE. I think what he's saying is that there—that there are lots of different kinds of Salmonella——

Mr. VOLKMER. Right.

Mr. GORE [continuing]. And that most of the kinds—most of the kinds that produce the illness that—that is commonly associated with Salmonella——

Mr. VOLKMER. Diarrhea.

Mr. GORE [continuing]. Do not—do not persist in—in human hosts, but are acquired from—from an animal population. But——

Mr. VOLKMER. That's what I'm getting at.

Mr. GORE [continuing]. But there are some other types of Salmonella that—that will persist in the human population. Is that——

Dr. COHEN. It may be possible. We don't know the epidemiology of all Salmonella serotypes——

Mr. VOLKMER. Yeah.

Dr. COHEN. We did do one study of Salmonella typhimurium and newport several years ago where we followed the introduction of a strain which had contaminated precooked roast beef and then showed that there was about a 10 percent frequency of individuals passing that organism on to other individuals, so it can occur and there may well be other species-specific strains. We don't know the epidemiology of all strains.

Dr. SABATH. If I may just add to that point, in looking over some material in preparation for coming here, I read recently that the average duration of carriage of Salmonella in humans after infection is about 5 weeks. It's generally pointed out, as Dr. Cohen very nicely did, that with Salmonella typhi, carriage for long periods of time is well established. Our general teaching has been that with the 2,000 other species, it is usually not carried by man for any great length of time, so I was rather surprised to read—I don't know if you'd comment—that about 5 weeks is considered the average carriage of species other than typhi. I just read that, but would you agree with that?

Dr. COHEN. Yes.

Mr. VOLKMER. Dr. Hays.

Dr. HAYS. Could I make one comment relative to the carriage state? We'll sample many animals and find that they're not shedding Salmonella. We stress those animals and they will shed Salmonella then. Now, I wonder if the same thing doesn't happen in people, in that frequently you'll hear of an outbreak that's following a long stress, a long trip or something and you attribute it—"Well, I picked that up in Hong Kong or Honolulu or somewhere," and it may have been—you may have had the organism in your system. Maybe the stress that you've underwent and—has triggered the proliferation of that organism. So I'm not sure that we really have the answer on carriers, how frequently humans might be carriers of Salmonella if they were really stressed.

One other point I'd like to make relative to the children and so forth. Children 1 year of age, you know, put everything that they get in their mouth and I think that that is one of the explanations. As I mentioned in my statement, we have an estimated 43 million pets and as they range around the neighborhood, they can certainly be carriers of the Salmonella organisms. So I think that in addition to meat, we have other animal sources of the Salmonella organism.

Mr. VOLKMER. You mean dogs and cats?

Dr. HAYS. Dogs, cats, birds and so forth.

Mr. VOLKMER. All right. The last thing—I guess I still have one—sorry, Mr. Chairman—if I may indulge. On the outbreak of the Salmonella newport, which is—basically dates back to the dairy farm—at least to a calf that had been there—has—that was when, in 1982, when the calf was slaughtered and——

Dr. COHEN. Yes.

Mr. VOLKMER [continuing]. And preserved. Have any further studies been made of that dairy herd, if it still exists?

Dr. COHEN. I don't—I don't know. I'd have to respond to that——

Mr. VOLKMER. Do you have any——

Dr. COHEN [continuing]. For the record.

Mr. VOLKMER [continuing]. Reservations about that dairy herd?

Dr. COHEN. As to whether or not it may be a continuing source of Salmonella?

Mr. VOLKMER. Yes.

Dr. COHEN. I think that as long as the milk products from that herd are pasteurized, that they are generally rendered safe. As with any other type of raw product, anyone who consumes raw milk is at a risk to acquire infections that are of animal origin. So, you know, I think that in itself doesn't represent a public health risk.

Mr. VOLKMER. Well, my only problem with that is, you know, dairy herds, as those dairy cows get a little older, they're sold—slaughtered, and all that meat usually goes to hamburger. Now, that's my problem with what you just said because when they cull those cows, they go to slaughter.

Dr. COHEN. Uh-huh.

Mr. VOLKMER. Have you had any further outbreaks up there?

Dr. COHEN. Not of this strain. We certainly do have other outbreaks of Salmonella newport——

Mr. VOLKMER. Right, but not of that strain and not in that area.

Dr. COHEN. No. Not that I'm aware of.

Mr. VOLKMER. Now, my question, then, is how long does the Salmonella, if it's in that herd and has infected that herd, what's preventing it from continuing to affect that herd?

Dr. COHEN. Well, perhaps Dr. Hays would like——

Mr. VOLKMER. If their resistance—if the resistance from subtherapeutic has been there and is in that livestock in that area, why isn't it continuing to affect?

Dr. COHEN. Well, let me—let me point out one thing before I turn it over to Dr. Hays because I think he's better to answer the questions about the effect in the animal population. Part of the analysis of the other strains of Salmonella newport indicated that the plasmid that was found by itself was also present in other strains with additional plasmids, that you can almost trace a path that this organism might have followed in coming up from Texas and infecting other populations. So this type of phenomenon is probably occurring all the time where we have strains that are evolving, changing, being spread from herd to herd, from animal group to animal group.

Mr. VOLKMER. Well, we don't know that.

Dr. COHEN. Well, from this data, we do. We can—we have some 10 other animal populations that have a similar organism.

Mr. VOLKMER. Where do they exist?

Dr. COHEN. They had—from Texas up into the Midwest area.

Dr. O'BRIEN. Apropos of that, when we first did our somewhat selective survey on animal isolates of Salmonella and human isolates, looking for—really using them just as ways of finding the same plasmids, we found that same plasmid—that extended slide with the diagram that had 53—those came from the—the majority

of the animal isolates there containing that same plasmid, or minor variations of it, were from, I think, 11 different States. Those were predominantly cattle isolates from 11 different States, and they accounted, again, with some crudity in the numbers, something like 11 percent of all the Salmonella isolates in the—this was a veterinary collection of isolates, and that veterinary collection from those 11 States. So that—there was that example, at least, of a—to illustrate the point that there is some evidence that individual plasmids or their families can get fairly widespread through—through herds in multi-States.

Mr. VOLKMER. Dr. Hays.

Dr. HAYS. It's probably not likely that dairy animals moved from Texas up to South Dakota and carried that with them——

Mr. VOLKMER. I agree with that.

Dr. HAYS. The organism could have come, and certainly, you're right that the cull—this is the reason we were raising questions about whether trying to exactly tie the beef to that beef farm, as it could very well be that a culled dairy cow or culled bull calf—not many of the bull calves are retained for—in the herd—so usually those go to market right away.

I forget what the orig—oh, the continuance of the Salmonella in that——

Mr. VOLKMER. Yes.

Dr. HAYS [continuing]. Here, as I understand—and I don't think. This was reported in the—in the paper itself, but from—I'd say—to me, it was a rumor, but I've heard that private communication with Dr. Holmberg is that the Salmonella isolate was found in that dairy cows after—at the time that they were investigating the people. Also, I understood that from these conversations, that one package of hamburger meat was found—one small package, and it was cultured and it was found to be negative.

At—but Salmonella in animals are pretty—it's a transitory thing. They're sick and then it passes. They get over it and they stop shedding it, but our work would say, "Well, hidden in those villi of the intestinal tract, there may be a few resident Salmonella there that could last for a long time, but it might never, never be triggered to cause a problem again." But it would be multiplying very, very slowly and remain there, but it usually would go down—the numbers that were being shed would reduce very rapidly in a relatively few days, just like it is in man.

Mr. VOLKMER. Thank you, Mr. Chairman.

Mr. GORE. Mr. Glickman.

Mr. GLICKMAN. Thank you, Mr. Chairman. I'll try to be brief. I hope that these questions haven't been asked before because I had to leave for a bit.

I would like one of—or all of you—perhaps Dr. Cohen, to talk about the difference again between therapeutic and subtherapeutic drugs. I want to make sure that these epidemiological tests and studies do, in fact, take into account the use of therapeutic drugs on animals and I wonder if you all, in this study or in any other studies, have tried to define the extent to which the problem may have been caused by therapeutic, as opposed to subtherapeutic usage of antibiotics and is there a way for you to define and separate those out when you make your studies?

Dr. COHEN. This particular beef herd had not received any therapeutic concentrations of antimicrobials. It had only been receiving subtherapeutic.

Mr. GLICKMAN. So then, your experience has been solely with respect to the subtherapeutic.

Dr. COHEN. In this particular—in this particular herd, that was all the farmer told us that he had used.

Mr. GLICKMAN. OK. Have you or anybody else done any studies on the issue of therapeutic applications of drugs or antibiotics in connection with this same problem?

Dr. COHEN. Well, there—I think we have to separate the epidemiologic studies that follow diseases that emerge in animals and so do humans to prospective studies that are conducted to examine differences in bacteria in controlled animal populations and Dr. Hays is probably the best to describe that.

In 1976, we investigated an outbreak—in the mid-1970's, we investigated an outbreak in Connecticut in which a farmer had purchased some—some calves that he was using in a veal operation. The calves were ill when they arove—or when they arrived at his—his farm. He used therapeutic antibiotics, subtherapeutic antibiotics. These organisms—these calves were infected with a multiresistant Salmonella heidelberg, which subsequently affected both the farmer and his daughter. The daughter was 9 months pregnant at the time and went to a neighboring hospital where she delivered, and transmitted the infection to her infant, who then was the source of infection for two other——

Mr. GLICKMAN. This isn't the——

Dr. COHEN [continuing]. Infants in the nursery.

Mr. GLICKMAN [continuing]. Farmer's daughter story, is it?

Dr. COHEN. It's the only one I know. [Laughter.]

Mr. GORE. You're not under oath. [Laughter.]

Dr. COHEN. So this—here is an instance where there's been exposure to both therapeutic and subtherapeutic, that I'm familiar with where there's transmission.

Mr. GLICKMAN. Can you tell me what the level of difference is for therapeutic and subtherapeutic? Is it on the basis of one injection? Is it a sustained period of injections?

Dr. COHEN. Why don't we turn that to Dr. Hays——

Mr. GLICKMAN. Five cc's versus 100 cc's or——

Dr. HAYS. Dr. Crawford's in the audience; I'd like for him to make that distinction. [Laughter.]

Mr. GLICKMAN. Well, perhaps one of the later witnesses will talk about this. I just—I just——

Dr. HAYS. It's not a clear—I don't want to be facetious. It's not a clear cut—what is therapeutic in one situation might not be high enough for therapeutic action in another situation and some of the levels that are being used that are called subtherapeutic might be considered therapeutic in certain situations.

Mr. GLICKMAN. Dr. O'Brien.

Dr. O'BRIEN. I just kind—suggested that subtherapeutic, again, is toward the effect on the animal. In terms of influencing all the events, the complicated events that happen within populations of bacteria, I think there's some evidence to suggest that there may

not be a distinction, that the bacteria treated with an antibiotic—they can't tell whether it's therapeutic or subtherapeutic.

Mr. GLICKMAN. It does—it seems to me that this scenario that requires—will require a great deal more testing and study because of the definitions between the two.

Now, Mr. Volkmer was asking about the—what other kinds of diseases that could be a serious health hazard and I think that there was some exchange between you and Mr. Volkmer.

What I'm curious about—maybe you talked about this before—is it your allegation or your belief that the use of subtherapeutic drugs makes humans less resistant to other nonanimal types of diseases?

Dr. O'BRIEN. Yes; I think you could say, in general, there looks to be—the way I would visualize it—populations of bacteria in animals, or in humans fed antibiotics, go through these evolutionary processes of developing plasmids and resistance genes, but they then are so fluid in their ability to migrate through other strains of bacteria that—that it's hard to say that any bacterial illness anywhere that has an antibiotic resistance—it's hard to sort out in the contribution of the—thinking backward to the genesis of that resistance what part of it was due to human antibiotic usage and what part might have remotely been due to antibiotic usage in animals.

Mr. GLICKMAN. Is there data to support your feeling? What I'm trying to get at is that you become more susceptible to polio, to measles, to——

Dr. O'BRIEN. No; those are viral.

Mr. GLICKMAN. OK, well, let's get some——

Dr. O'BRIEN. Well, I think the kinds of bacteria you're concerned about are bacteria such as——

Mr. GLICKMAN. Encephalitis, meningitis.

Dr. O'BRIEN. Meningitis—meningitis, hemophilus group B does have the major problem in that. That would be the amipicillin resistance, which has been a substantial problem, and that is widespread on certain plasmids in—in humans—in human populations of bacteria, and also very widespread in animals. So the genesis of it is lost to us, but it's—we'll never be able to reconstruct the history of that, but at least it is a gene in humans—troublesome in a different strain of human bacteria—that you can't say didn't have some of its genesis in animal populations.

Mr. GORE. If my colleague will yield just briefly, one of the reasons why we're having 2 days of hearings—one on use in livestock and the other involving the practices of physicians using antibiotics in humans is because we were advised by many people in looking at this whole subject that—that it ought—the subject ought to be defined as antibiotic resistance, and we ought to look comprehensively at all the factors that might be contributing to it.

A background of that problem, which really hasn't been laid out here yet, is that there is a—a progressive loss in the—of the effectiveness of antibiotics that have been prescribed in humans for the last 40 years. Now, I'm right on that, aren't I? I mean, in all these diseases that—that antibiotics are used to attack, there is a race to invent or discover new, more powerful and more effective antibiot-

ics as there is a progressive loss in the effectiveness of those that have been used.

So the question really is: What is it that is—that is making the antibiotics less and less effective? The natural evolution of the—of the bacteria is clearly a part of it. The artificial selection of the resistance genes, which comes from large use of antibiotics in humans, is clearly a part of it, and the artificial selection of resistance genes that comes from the large use of antibiotics in one of our major sources of food supply is clearly part of it.

Now—but I just wanted to interject at that point because it occurred to me that we really hadn't stated early on in the hearing that this is—this is the basic problem, and that is, that our antibiotics are losing their effectiveness.

Dr. O'BRIEN. Let me make—just add one to your category just for the sake of completeness. It may come up tomorrow. The other thing is that it is now, I think, emerging that the problems of antibiotic resistance tend to be worse in developing countries for a number of reasons: lack of infrastructure to work around it and so on; maybe overuse, poor use of antibiotics——

Mr. GORE. They're over-the-counter drugs there, also.

Dr. O'BRIEN. Over-the-counter drugs, a very important one, and another source of resistance genes in plasmids for patients in this country, it is some to extent—this has been documented—is plasmids and genes that seem to have been developed in other parts of the world, or at least first appeared in other parts of the world—being introduced into this country.

So that's another compartment, I think, one can look at where antibiotic usage practices differ, generating genes and plasmids that will show up all over the world ultimately. So I think that's another element of it that ought to be included if you're making a complete description.

Mr. GORE. I thank my colleague for yielding.

Mr. GLICKMAN. I think—Dr. Sabath, did you have a comment or——

Dr. SABATH. Yes, if I may. I'd like to just make a comment for this committee related to the concern that Mr. Gore very beautifully summarized, and it's also in Dr. O'Brien's remark—namely the fear that many of us had in the late 1960's and around 1970, was exactly what you said. Is it possible that using these low levels of antibiotics in animals selects a pool of resistance genes that eventually get transmitted to man in our food—even though it may not be causing disease, but while residing in man now becomes the source of resistance genes in other germs—and Dr. O'Brien just mentioned some—that have nothing to do with animals? That was the fear, and a British worker named Anderson, in the late 1960's, was a great exponent of this.

And there's an enormous controversy then, and I'd have to say that I would have, at that time, said, "I don't know what's happening," but we already have the experiment that's been done in Britain. That is, if you stop using it altogether for subtherapeutic use, will this make any difference? I don't think any of us would have known that if that experiement hadn't occurred. It's now occurred.

I quoted from Linton's work and others, that it made no difference whatsoever by singling out that single use because all of these

other uses of antibiotics are continuing to play on the selective process.

Now, I personally have no reason to suspect that if we did limit the use in this country our results would be any different than what happened in Britain in the last 12 years, and if I may, I'd like to ask Dr. Cohen, since his article suggested that maybe that's an important problem, would he have any reason to think it'd be any different in this country than it was in Britain in the last 12 years where we've already seen that experiment?

Dr. COHEN. Well, again, I'm not sure how it's been enacted in Britain, whether it's really been effective, and if there was something that would be so done in this country, I think it would have to be a tremendous consideration of any activity as to whether or not what actions are going to be taken are going to be effective.

Mr. GORE. Let me—let me jump in here just a second with my colleague's indulgence. What I said earlier was not meant to imply that human beings were absorbing these gene resistance—these resistance genes and plasmids by consuming the meat. I think there is—there's clearly some uncertainty about what vectors are transferring the resistance genes from the bacteria in animal populations to the bacteria in human populations. Now, the—the example that Dr. Cohen has cited with his detective work is persuasive to me that in that case, there was a vector following the path of consumption, but there are other vectors as well which are causes for concern about the transfer of plasmids from one population to another, and if gene—if resistance genes are—are easily transferrable, as they seem to be, between different species of bacteria, then clearly that's a—that's a very serious problem for public health, and overuse or misuse of antibiotics in both animals and humans would—would be a very shortsighted practice if it results in the progressive weakening of the—of the antibiotics and—and a deterioration in their usefulness to it—to us.

Anyway, excuse me. Go ahead.

Mr. GLICKMAN. Let me just ask a couple more quick questions. I'm going to ask this one of Dr. Hays. The evidence seems to be that in promoting growth, antibiotic additives also enable farmers to use less feed to produce more meat. Is that a fair statement?

Dr. HAYS. Yes, sir.

Mr. GLICKMAN. Do you have any idea how much less feed, either in a—in a—per animal or in an aggregate sense?

Dr. HAYS. Well, the estimated reduction in feed efficiency, say, in pigs, is around 4 to 5 percent less feed to get the pigs to market weight, and it's not too much different from that in—in poultry, so that's about——

Mr. GLICKMAN. So if the figures—as I understand it, nearly all poultry, 70 percent of cattle and 90 percent of pigs raised commercially in the United States ingest subtherapeutic doses of antibiotics at mealtimes. If that's the case, then we're probably using 5 percent less feed than we would ordinarily be using.

Dr. HAYS. I wouldn't say that all the animals—all those are subjected to subtherapeutic use. Most of them are subjected to antibiotics somewhere along the life cycle, but it's not necessarily subtherapeutic use.

Mr. GLICKMAN. OK. I'd like to ask another question in connection with the British experiment that you talked about.

I'm told that throughout the continent of Europe, antibiotics that are used in human therapy, like the tetracycline group, are banned from animal feed and that's been the case since 1976. That's not only in Britain, but it's all throughout the EEC. Is that correct?

Dr. HAYS. I'll tell you, we have trouble getting data on, say, what percentage of antibiotics are used in animals here in this country and what goes in human medicine, and the records—our records are very, very good from what you can come up with other countries, and so I think it's a lot of guesswork as to really what is happening.

We—some of the Common Market countries will claim to do this. Their regulations are very good, but no one is monitoring it, so they're using drugs pretty much as they wish, rather than as they are regulated, and we do not have that kind of system——

Mr. GLICKMAN. Well, I guess my curiosity—perhaps Dr. Cohen might know this, I don't know—have there been formal legislative or regulatory decisions in Belgium and the Netherlands and France and Germany that have banned the use of human antibiotic additives like the tetracycline group for animals?

Dr. HAYS. The Common Market countries have in general adopted the same policies. I think maybe Spain was the last one to come on to the——

Mr. GLICKMAN. OK, I'm told that FDA representative in the next panel may be able to go into that one greater in depth.

Final question is that—and this is a subjective question—if you all here were going to make recommendations to the FDA in connection with either Dr. Cohen's subject of—or the subject of the New England Journal article that you've testified to or the subject in general about the use of subtherapeutic drugs, antibiotics in animals, what would you recommend? Nothing, more tests, banning them, or something in between? Studies—I said more tests—could be one of them.

I wonder if you'd go down the line and just tell me what you think.

Dr. COHEN. OK. Let me first say that in my opinion, because CDC has no formal recommendations as to what FDA does in this matter, I think that the various chain of events are well documented, that one uses antimicrobials, one develops resistance, organisms are transmitted from animals to man. I think with this kind of knowledge that one has to look at some limitations on the use of these agents, both in animals and in humans, and so I think my recommendation would be to consider the various uses that are required by industry, and with those types of requirements, try to develop some appropriate regulations or guidelines to restrict the use of these agents.

Mr. GLICKMAN. Dr. O'Brien?

Dr. O'BRIEN. I think I am a bit reluctant, as someone working to try to get data one way or the other, to become precommitted to what's essentially a policy decision; I think it's probably not a good thing for the people who are trying to look at data arbitrarily objectively to forecast policy. And I think that I can delimit the areas

that I feel fairly strong about and the others that I really am not as confident about.

I feel that what we have accomplished is—and this is the area that I'm most familiar with, at least, is establishing that the antibiotics—resistance pools, plasmids, and genes, of animals and animal bacterial populations in humans—are common. They do interconnect. I think that's something that we didn't know several years ago.

And I think—my suspicion is that although this isn't documented yet—this is projected really with the ease with which we were able to find several examples, and if one were to do it more thoroughly, my projection would be that you'd have a fairly substantial interconnection. It wouldn't be just occasional and trivial, that a significant—whatever that means—a significant contribution of the resistance pool, the genetic pool of humans does come from animals—is contributed by animal bacterial populations or has its—some part of its genesis in animal bacterial populations, both perhaps in number of transfers of individual genes and in the whole evolutionary process that conceivably moves back and forth between the two. So I think that's a substantial consideration.

I think it will then come down to the two other considerations which will be the cost benefit—what does this cost in terms of patient care and medical expense and so on, which would be hard to put a number on at the moment, I think, although I think it's not—it will turn out to be significant. And that has to be balanced against the costs to the agricultural process of a ban and the questions that Dr. Hays raises and I think we can be concerned about—from what we know about how bacteria and plasmids behave generally, the efficacy of a ban, keeping in mind that banning the certain antibiotics in animal feeds might—in other words, you may not get from banning it now what you would have gotten if you hadn't used them in the first place.

That's another variable that I don't think is completely—so I think the policy will have to be cost/benefit, looking at those two ends of it. I think that we now know they're connected, and we can no longer say they are unrelated. They are connected and it's a question of trying to put, first of all, some quantitative values at either end and then, however policymakers decide between values.

Mr. GLICKMAN. Thank you. Dr. Hays.

Dr. HAYS. Well, I hate to just suggest that we continue this debate for years and years and years, but I do think there are some critical studies that have not been accomplished as yet, and that is to try and really get at how much of the transfer of the resistance is from man to animals. The National Academy of Sciences suggested some studies that would have possibly helped answer that, say, meat-eaters versus nonmeat-eaters and those people that work with animals on a very regular basis versus those that have no contact with animals.

I think some of those studies that were suggested by the National Academy of Sciences panel would provide us more solid—more solid basis for making changes that would be effective.

Mr. GLICKMAN. Thank you. Dr. Sabath.

Dr. SABATH. I don't believe there's sufficient data available to justify any major change in national policy at all concerning this

matter. It'd be nice to say that I know exactly what we should do, however, the problem of resistant bacteria—and, of course, an enormously important one, and I think probably more Federal support for looks at basic aspects of antibiotic resistance would be in order. A large fraction of such work is being supported by the pharmaceutical industry, but I think basic work in here should be more heavily supported by the Government.

One of the—two of the suggestions that have been made—although I don't think either are practical at the moment—one is the banning of use for subtherapeutic. We've talked about that this morning. The second, which hasn't really been elaborated on here this morning, but has been in the scientific press, is using totally unrelated antibiotics for veterinary use, as we use in human use. I think ideally that would be wonderful if we could come up with those—that many superantibiotics, but we're occasionally even changing our mind regarding what we use for man, where now one of the highest dollar-amount used antibiotics was considered basically over the hill 20 years ago, but changes in resistance have made this now a very popular one.

So although theoretically I think that would be good, I don't think we have such agents now, that we have such a plethora that we can totally say these are only for animal and these are only for man, but that has been suggested. So I think the bottom line is I think we need—we need more work. I don't see anything that even suggests justification of a major policy change on the basis of what we now know.

Mr. GLICKMAN. Thank you very much. Thank you, Mr. Chairman.

Mr. GORE. Let me ask the three nongovernment people here, do any entities or companies with interests in this question provide research funding to you or your institutions?

Dr. O'Brien?

Dr. O'BRIEN. No.

Mr. GORE. Dr. Hays?

Dr. HAYS. We have no support right at the present time for this comprehensive microbiological study that we're doing other than the State support from our institution. Now, in our total program of—in a department of 50 faculty members, we do have some various grants of—from commercial companies supporting part of our research on other facets of our total research program.

Dr. SABATH. Yes; I'm receiving support from several pharmaceutical firms for research on antibiotic resistance in man and some basic aspects, but nothing related to use in agriculture.

Mr. GORE. All right. All right. There are a lot of other questions that we could go into, but——

Mr. VOLKMER. Mr. Chairman.

Mr. GORE [continuing]. The time is—we've got a whole bunch of other witnesses.

Mr. Volkmer.

Mr. VOLKMER. I just wonder, are we going to have some witnesses in regard to the Seattle-King County study?

Mr. GORE. Yes.

Mr. VOLKMER. Yes; we will.

Mr. GORE. Yes; we are.

Mr. VOLKMER. Could I ask a couple quick questions? One of Dr. O'Brien?

Mr. GORE. Yeah.

Mr. VOLKMER. And——

Mr. GORE. We really need to move on, though, because this panel——

Mr. VOLKMER. I realize that——

Mr. GORE [continuing]. Has lasted a long time.

Mr. VOLKMER [continuing]. And I was wondering if he could make a comment on the study that was made in England that Dr. Sabath had alluded to in regard to following the discontinuance of the use of the subtherapeutic antibiotics and the showing there of still a continuation and a very little decrease in the bacteria.

Dr. O'BRIEN. I'm not sure. Which—I—I know—I've heard that——

Mr. VOLKMER. You had the chart up——

Dr. O'BRIEN [continuing]. Reported, but I don't know of a specific—oh, that's right, you had a table. What was that from? Was that Alan——

Dr. SABATH. From Linton.

Dr. O'BRIEN. Al Linton.

Mr. VOLKMER. Have you had an opportunity to examine that study and that report?

Dr. O'BRIEN. I've seen it in the past. I—the details aren't clear to me now.

Mr. VOLKMER. All right, fine, then you don't wish to comment on it then?

Dr. O'BRIEN. No.

Mr. VOLKMER. Right. All right.

The other thing I'd like to ask, Mr. Chairman, ask very briefly, Dr. Cohen and Dr. O'Brien, the beef herd that was up there in South Dakota had had subtherapeutic antibiotic use; is that correct?

Dr. COHEN. Oh, yes.

Mr. VOLKMER. Now, if it had not had it, would we have had—assuming that it was a generation of the bacteria that caused the problem, if it had not been used, would we have the same result, assuming all the other things are true in your chain of events?

Dr. COHEN. Well, I can't say in the sense that if there were no persistence of infection, the organism might have been eliminated from the population prior to going to slaughter so you might have had three isolated cases or four isolated cases in South Dakota with no additional cases. I'm just—I have nothing to base that on in the way of data. I'm just speculating.

Mr. VOLKMER. Well, my question is: If we assume that the herd—and I'm assuming that you're assuming that the herd—beef herd—was affected from the dairy herd. Is that correct?

Dr. COHEN. I can't say. It might have come in either direction.

Mr. VOLKMER. So you're not saying what the starting point was, then?

Dr. COHEN. That's correct. All we know is that an organism similar to this organism had been in the continental United States for some period of time prior to its infection in this animal population we're talking about and it underwent a subtle change in losing a

small plasmid which allowed us to identify it. And at that point, we're—it had interchanged and who—which animal population acquired the infection first, I can't say.

Mr. VOLKMER. And so you're not able to say, either, whether we would have had that infection within that herd if you hadn't had the uses of subtherapeutic antibiotics in that herd?

Dr. COHEN. That's correct.

Mr. VOLKMER. All right.

Mr. GORE. Thank you.

Thanks to all of you for—for your testimony here. We appreciate it very much.

I'd like to call our next panel now and I appreciate the patience of all the witnesses because this is taking more time than I had thought it would.

I'd like to call Dr. Lester Crawford to the witness table, Director for the Center—Director of the Center for Veterinary Medicine at FDA; and Dr. Donald Houston, Administrator of the Food Safety and Inspection Service at USDA.

Gentlemen, without objection, your prepared statements will be included in full in the record at this point. If you'd care to summarize any parts of your statements, feel free to do so.

Dr. Crawford, we're honored to have you here and please proceed.

STATEMENTS OF DR. LESTER CRAWFORD, DIRECTOR, CENTER FOR VETERINARY MEDICINE, FOOD AND DRUG ADMINISTRATION; AND DR. DONALD HOUSTON, ADMINISTRATOR, FOOD SAFETY AND INSPECTION SERVICE, U.S. DEPARTMENT OF AGRICULTURE

Dr. CRAWFORD. Thank you.

I welcome this opportunity to discuss with you and the subcommittee the views of the Center for Veterinary Medicine of the Food and Drug Administration. The Center has been concerned for some time about the possible health hazard posed by the use of antibiotics in animal feed. In particular, the Center is concerned about the long-term subtherapeutic uses of antibiotics in feeds.

These are used for improving feed efficiency and rate of weight gain and for disease prevention. Because these uses promote the development of drug-resistant bacteria in animals and routes for the movement of these resistant bacteria to man are available, we believe that drug resistance and the bacteria associated with the food animals can affect the proportion of drug-resistant bacteria that cause human diseases. Therefore, the potential exists for compromise in drug therapy in animals and in humans.

In late 1977, the Bureau of Veterinary Medicine, now the Center for Veterinary Medicine, published proposals in the Federal Register to restrict the addition of low levels of certain antibiotic drugs to animal feed. These drugs are penicillin, two tetracycline drugs [oxytetracycline and chlortetracycline] and combination products containing these antibiotics.

Penicillin and the tetracyclines were chosen because of their importance in the treatment of human disease. The Center's concern that the continued unrestricted subtherapeutic use of these antibi-

otics presents risk to human and animal health is based upon considerations of a number of factors. Continued unrestricted subtherapeutic use of antibiotics in animal feed increases the pool of drug-resistant bacteria in our environment. Moreover, the prospect of pathogens becoming drug-resistant is a real threat to human health. This risk is demonstrated by the recent emergence of human diseases caused by antibiotic-resistant bacteria.

In short, the evidence suggests that enteric microorganisms associated with food animals and man, their R-plasmids, and human pathogens form linked ecosystem in which action at any one point can affect every other. If the vulnerability of microorganisms to antibiotics is reduced by the use of antibiotics for nonmedical purposes in animals, the effectiveness of medical treatment will be diminished in man.

Potential risks to animal health also exist and while the linkage to human health is indirect, animal agriculture faces a risk directly. The development of resistant strains, which is enhanced by subtherapeutic drug use, reduces the efficacy of these same drugs for the treatment of animal diseases.

If I could, I'd like to describe where we are today on this issue and how we got there. Since the early 1950's, the practice of using low levels of antibiotics in animal feeds has steadily increased, particularly in the feeding of beef cattle, poultry, and swine. Soon after the feeding of low levels of antibiotics to animals became popular, scientists in the United States and in other countries began studying the effects of the practice and very early on expressed concern about the continuous long-term usage of low levels of antibiotics.

Between 1970 and 1977, FDA had directed several groups to review the use of antibiotics in animal feeds. As a result of those studies and these groups' recommendations, the Commissioner of FDA determined in 1977 that the Center should proceed with proposals to withdraw the subtherapeutic uses of penicillin and the tetracyclines from animal feeds, both alone and in combination. Low level use of the tetracyclines was to be eliminated except where no substitutes were available.

In 1977, the former Director of the Bureau of Veterinary Medicine stated the statutory procedures for revoking present approvals when he published in the Federal Register detailed proposals to withdraw subtherapeutic uses of penicillin and the tetracyclines from animal feeds with the corresponding notices of opportunity for hearing.

In 1978, the Congress allocated money for a study of the entire antibiotics in animal feeds issue to be conducted by the National Academy of Sciences. The House Appropriations Committee, in its report on FDA's appropriations, also stated that FDA should hold in abeyance any implementation of the proposed withdrawal action pending completion of the study.

In addition to the NAS report, other congressionally mandated studies were completed, including a 1978 report by the U.S. Department of Agriculture and a 1979 study by the Office of Technology Assessment. These reports essentially supported the agency's scientific concerns.

On March 18, 1980, the National Academy released its report of the effects on human health of subtherapeutic uses of antimicrobials in animal feeds prepared by its committee to study the health effects of subtherapeutic antibiotic use in animal feeds. The NAS Committee concluded that existing data had neither proved nor disproved the postulated hazards to human health from subtherapeutic antimicrobial use in animal feeds.

The NAS Committee also stated that the lack of data linking human illness with the subtherapeutic use of antimicrobials must not be equated with proof that hazards do not exist. The NAS Committee stated that the research necessary to establish and measure definite risk had not been conducted. However, in the committee's opinion, it was not possible to conduct a single comprehensive epidemiological study of the effects on human health resulting solely from the subtherapeutic use of antimicrobials in animal feeds.

The NAS Committee suggested several less comprehensive but more feasible studies that had the potential to clarify certain points, although not all issues would be settled. It was hoped that the suggested studies would better define the links in the chain of events that is believed to exist from the feeding of subtherapeutic levels of antibiotics in animals to the development of drug-resistant disease in humans.

In the appropriations report for fiscal year 1981, the House Appropriations Committee provided money in FDA's budget for a definitive epidemiologic study of the antibiotics in animal feeds issue. Again the committee stated that FDA should hold in abeyance any implementation of the proposed withdrawal pending completion of the studies and reevaluation of FDA's concerns.

In response to the congressional mandate to generate additional data, FDA awarded a contract to the Seattle-King County Department of Public Health to conduct an epidemiological study of Salmonella and Campylobacter in commercial meat products in the community and their association with human disease.

In August of this year, the Center received the final study report which has been accepted as having met contractual obligations. This study, along with other studies conducted under FDA contract, is currently undergoing scientific review by the Center's staff. We're also conducting a worldwide literature search to review all available research and other information.

The 1977 proposed withdrawals were criticized on the grounds that there was not adequate epidemiologic evidence demonstrating that drug-resistant bacteria of animal origin are commonly transmitted to humans and cause serious illness.

In addition, there were no specific instances in which the feeding of subtherapeutic antibiotics to animals was associated with the subsequent development of disease in humans. We believe that recent data contributes significanly to our knowledge of the subject.

With regard to the several studies that have been mentioned earlier, I will not particularly comment on. However, we have released for public consumption the Seattle-King County study prior to its final peer review, which is now being undertaken within the Center for Veterinary Medicine.

I had mentioned that earlier and I would now like to discuss certain aspects of it. The study was designed to determine the relationship between the occurrence of human diarrheal illness caused by Salmonella and Campylobacter organisms and the occurrence of these bacteria in foods of animal origin. Thus, Salmonella and Campylobacter would serve as models to estimate the flow of bacteria from animals to man through the food chain.

The study used a dual surveillance approach, one monitoring cases of human illness and the other involving the sampling of meat for contamination. For human case surveillance, all cases of Salmonella and Campylobacter enteritis diagnosed in enrollees at Group Health Cooperative of Puget Sound, a 320,000-member health organization, were investigated over an 18-month period. Control subjects for Campylobacter cases were also investigated; food surveillance was integrated into the Health Department's meat inspection program and thus provided access to all retail purveyors of meat products in King County, WA.

Added to the retail meat surveillance system was a specification for culturing poultry products at a large independent poultry processor in Seattle. In order to evaluate relationships among individual Campylobacter and Salmonella isolates, antibiotic susceptibility testing was conducted along with serotyping and several types of plasmid analyses.

The next development, in addition to this study, and also the two studies previously discussed by the former panel, is the petition on the imminent hazard to public health of the use of penicillin and tetracycline in animal feed.

On November 20 of this year, Secretary Heckler, of the Department of Health and Human Services, received from the Natural Resources Defense Council a petition to declare the subtherapeutic uses of penicillin and the tetracyclines in animal feeds an imminent hazard to the public health. NRDC argues that, on the basis of three recently published scientific studies—the O'Brien and the two Holmberg studies discussed earlier—FDA is likely to eventually withdraw approval of the subtherapeutic uses of penicillin and the tetracyclines in animal feeds.

NRDC argues, based on these studies, that these uses meet the criteria for imminent hazard under the law. Before making any recommendation to FDA Commissioner Young, and then to Secretary Heckler, I believe the center must evaluate all available information and not just the three studies cited before deciding on the petition. To assist in identifying pertinent available data and information, FDA has decided to hold a legislative-type hearing in which interested persons are invited to present their views. This notice will be published in the Federal Register.

The criteria used to evaluate the petition will be: First, the likelihood that FDA will eventually withdraw approval; second, the severity of harm pending withdrawal of approval; third, the likelihood of harm pending withdrawal of approval; fourth, the risk to treated animals from suspended marketing; and fifth, other approaches to protect the public health.

After the legislative-type hearing, a recommendation on the petition will be formulated after the center has completed its review of results from FDA contracts, published literature, and other data

and information, especially that brought to our attention at the hearing.

Based on this review, the agency will make a recommendation to the Secretary, who has nondelegable authority to declare drugs an imminent hazard. If the agency decides to proceed with withdrawal, a formal evidentiary public hearing before an administrative law judge would be required. Under our law, such a hearing would be needed in this case even if the drug uses in question were to be found an imminent hazard, and even if FDA holds the legislative-type hearing on the imminent hazard petition.

Granting an imminent hazard petition does not avoid formal proceedings. Rather, granting a petition suspends the marketing of the drug immediately before the completion of the formal evidentiary public hearing, the administrative law judge's initial decision and the Commissioner's final decision.

Under the ordinary withdrawal procedures in which a drug does not meet statutory requirements, but does not present an imminent hazard, the drug may be marketed until the completion of all these steps.

In conclusion, Mr. Chairman, at the time of our original proposal to ban the subtherapeutic uses of penicillin and the tetracyclines in animal feeds, the contention was advanced that there were gaps in the scientific position to support a chain of events linking low-level antibiotic feedings to disease in humans. Since then, newly generated data have been useful in filling these gaps in our knowledge.

After we review and evaluate these new data, the agency will know whether to proceed with the proposed ban. From this review, along with a study of the information presented in the legislative-type hearing, the agency also will be prepared to make a recommendation to the Secretary on NRDC's hazard petition.

In sum, two decisions must be made in the near future: First, whether to move forward with the withdrawal proceedings; and second, whether the hazards to human health are of such significance as to call for an immediate ban of low-level uses of penicillin and the tetracyclines in animal feeds. Sometime in the spring, we expect to recommend that the Secretary grant or deny the imminent hazard petition.

This concludes my formal statement. I will be happy to answer any questions you or members of the subcommittee might have. Thank you.

[The prepared statement of Dr. Crawford follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT

BY

LESTER M. CRAWFORD, D.V.M.

DIRECTOR

CENTER FOR VETERINARY MEDICINE

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

COMMITTEE ON SCIENCE AND TECHNOLOGY

UNITED STATES HOUSE OF REPRESENTATIVES

DECEMBER 18, 1984

FOR RELEASE ONLY UPON DELIVERY

Mr. Chairman:

I welcome this opportunity to discuss with you and the Subcommittee the views of the Center for Veterinary Medicine (Center), Food and Drug Administration (FDA) on the proposed withdrawal of approvals for low level uses of penicillin and the tetracyclines in animal feeds.

Before offering specific comments on FDA's current and future activities in this area, let me first discuss why the Center is concerned about the continuous use of low levels of antibiotics in animals feeds, and what has happened since our original proposals in 1977 to withdraw these approvals. To supplement my testimony, I would like to submit for the record several documents that are relevant to this issue. A list of those documents is attached.

CONCERNS FOR ANIMAL AND HUMAN HEALTH

The Center has been concerned for some time about the possible health hazard posed by the use of antibiotics in animal feed. In particular, the Center is concerned about the long-term, subtherapeutic uses of antibiotics in feeds. These are used for improving feed efficiency and rate of weight gain, and for disease prevention. Because these uses promote the development of drug resistant bacteria in animals and routes for the movement of these resistant bacteria to man are available, we believe that drug resistance in the bacteria associated with food animals can affect the proportion of drug resistant bacteria that cause human diseases. Therefore, the potential exists for compromise of drug therapy in animals and in humans.

In late 1977, the Bureau of Veterinary Medicine (now the Center for Veterinary Medicine) published proposals in the Federal Register to

restrict the addition of low levels of certain antibiotic drugs to animal feed. These drugs are penicillin, two tetracycline drugs (oxytetracycline and chlortetracycline), and combination products containing these antibiotics. Penicillin and the tetracyclines were chosen because of their importance in the treatment of human disease.

The Center's concern that the continued unrestricted subtherapeutic use of these antibiotics presents risks to human and animal health is based upon consideration of a number of factors:

-- Long-term, low-level feeding of penicillin and the tetracyclines promotes, by natural selection from the pool of normal intestinal flora, those enteric (gut) bacteria that contain R-plasmids. R-plasmids, also known as R-factors, are extra chromosomal genetic material which confer antibiotic resistance to host bacteria. These plasmids can be transferred between various kinds of bacteria through cell-to-cell contact (conjugation). Simultaneous resistance to several unrelated antibiotics is commonly carried on a single plasmid and therefore is simultaneously transferred from one bacterium to another.

-- E coli strains bearing R-plasmids can be transferred from animal to man. Under the proper circumstances, organisms of animal origin can colonize in the human gut because the transfer event can occur within a short period of time, and it is only necessary for one transfer to occur. However, colonization is not considered necessary for transfer of drug resistance to strains that inhabit the human gut.

-- Factors associated with pathogenicity of E. coli have been shown to occur on the same plasmid as drug resistance, and drug resistance and pathogenic factors have been co-transferred from one bacterium to another.

-- R-plasmids can be transferred from normally nonpathogenic E. coli to certain pathogenic strains of bacteria with which they may come in contact in man or animals. Since R-plasmids carry drug resistance, this transfer can result in the creation of pathogenic strains of bacteria which are resistant to antibiotic therapy.

Continued unrestricted subtherapeutic use of antibiotics in animal feed increases the pool of drug-resistant bacteria in our environment. Moreover, the prospect of pathogens becoming drug resistant is a real threat to human health. This risk is demonstrated by the recent emergence of human diseases (e.g., gonorrhea, shigellosis, childhood meningitis, and pneumonia) caused by antibiotic-resistant bacteria.

In short, the evidence suggests that enteric microorganisms associated with food animals and man, their R-plasmids, and human pathogens form a linked ecosystem in which action at any one point can affect every other. If the vulnerability of microorganisms to antibiotics is reduced by the use of antibiotics for nonmedical purposes in animals, the effectiveness of medical treatment will be diminished in man. Potential risks to animal health also exist. And while the linkage to human health is indirect, animal agriculture faces the risk directly. The development of resistant strains, which is

enhanced by subtherapeutic drug use, reduces the efficacy of those same drugs for the treatment of animal diseases.

Let me describe where we are today on this issue and how we got there.

BACKGROUND

Since the early 1950's, the practice of using low levels of antibiotics in animal feeds has steadily increased, particularly in the feeding of beef cattle, poultry, and swine. Soon after the feeding of low levels of antibiotics to animals became popular, scientists in the United States, and in other countries, began studying the effects of the practice and, very early on, expressed concern about the continuous long-term use of low levels of antibiotics.

Between 1970 and 1977, FDA had directed several groups to review the use of antibiotics in animal feeds. As a result of those studies and these groups' recommendations, the Commissioner determined, in 1977, that the Center should proceed with proposals to withdraw the subtherapeutic uses of penicillin and the tetracyclines (chlortetracycline and oxytetracycline) from animal feeds both alone and in combination. Low level use of the tetracyclines was to be eliminated except where no substitutes were available. In 1977, the Director of the Bureau of Veterinary Medicine stated the statutory procedures for revoking present approvals, when he published in the Federal Register detailed proposals to withdraw subtherapeutic uses of penicillin and the tetracyclines from animal feeds with the corresponding Notices of Opportunity for Hearing.

In 1978, the Congress allocated money for a study of the entire antibiotics in animal feeds issue, to be conducted by the National Academy of Sciences (NAS). The House Appropriations Committee, in its report on FDA's appropriations also stated that FDA should hold in abeyance any implementation of the proposed withdrawal action pending completion of the study. In addition to the NAS report, other Congressionally mandated studies were completed including a 1978 report by the United States Department of Agriculture and a 1979 study by the Office of Technology Assessment (OTA). These reports essentially supported the Agency's scientific concerns.

On March 18, 1980, the NAS released its report, "The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds," prepared by its Committee to Study the Human Health Effects of Subtherapeutic Antibiotic Use in Animal Feeds. The NAS Committee concluded that existing data had neither proven or disproven the postulated hazards to human health from subtherapeutic antimicrobial use in animal feeds.

The NAS Committee also stated that the lack of data linking human illness with the subtherapeutic use of antimicrobials must not be equated with proof that hazards do not exist.

The NAS Committee stated that the research necessary to establish and measure a definite risk has not been conducted. However, in the Committee's opinion it was not possible to conduct a single, comprehensive epidemiological study of the effects on human health resulting solely from the subtherapeutic use of antimicrobials in animal feeds. The NAS Committee suggested several less comprehensive,

but more feasible, studies that had the potential to clarify certain points, although not all issues would be settled. It was hoped that the suggested studies would better define the links in the chain of events that is believed to exist from the feeding of subtherapeutic levels of antibiotics in animals to the development of drug-resistant disease in humans.

In the Appropriations Report for FY 1981, the House Appropriations Committee provided money in FDA's budget for a definitive epidemiological study of the antibiotics in animal feeds issue. Again, the Committee stated that FDA should hold in abeyance any implementation of the proposed withdrawal pending completion of the studies and reevaluation of FDA's concerns. In response to the Congressional mandate to generate additional data, FDA awarded a contract to the Seattle-King County Department of Public Health to conduct an epidemiological study of Salmonella and Campylobacter in commercial meat products in the community and their association with human disease. In August of this year, the Center received the final study report, which has been accepted as having met contractual obligations. This study, along with other studies conducted under FDA contract, is currently undergoing scientific review by the Center's staff. We are also conducting a worldwide literature search to review all available research and other information.

CURRENT INFORMATION AND DATA

The 1977 proposed withdrawals were criticized on the grounds that there was not adequate epidemiologic evidence demonstrating that drug-resistant bacteria of animal origin are commonly transmitted to humans and cause serious illness. In addition, there were no specific

instances in which the feeding of subtherapeutic antibiotics to animals was associated with the subsequent development of disease in humans. We believe that recent data contribute significantly to our knowledge of the subject.

O'Brien et al.

In this study, which was published in 1982, the researchers were able, using a new biochemical technique, to trace genetic components (R-plasmids) of various strains of Salmonella bacteria. The researchers found that the R-plasmids in some bacteria in man and food animals are genetically similar or virtually identical. They concluded that this similarity is evidence that antibiotic-resistant bacteria may be transmitted between food animals and man on a widespread basis.

Seattle-King County Study

I have already mentioned the contract awarded to Seattle-King County Department of Public Health, which I would now like to discuss. The study was designed to determine the relationship between the occurrence of human diarrheal illness caused by Salmonella and Campylobacter organisms and the occurrence of these bacteria in foods of animal origin. Thus Salmonella and Campylobacter would serve as models to estimate the flow of bacteria from animals to man through the food chain.

The study used a dual surveillance approach--one monitoring cases of human illness and the other involving the sampling of meat for contamination. For human case surveillance, all cases of Salmonella and Campylobacter enteritis diagnosed in enrollees at Group Health Cooperative of Puget Sound, a 320,000 member health maintenance

organization, were investigated over an 18-month period. Control subjects for Campylobacter cases were also investigated. Food surveillance was integrated into the health department's meat inspection program and thus provided access to all retail purveyors of meat products in King County, Washington. Added to the retail meat surveillance system was a specification for culturing poultry products at a large independent poultry processor in Seattle. In order to evaluate relationships among individual Campylobacter and Salmonella isolates, antibiotic susceptibility testing was conducted along with serotyping and several types of plasmid analyses.

The contractor reported that a significant proportion of poultry samples collected at retail outlets and from the poultry processing plant were contaminated with Campylobacter. Other meats had a much lower order of Campylobacter and Salmonella contamination rate. These complemented the results of the investigation of case and control subjects in that the contractor estimated that nearly one-half of all of the Campylobacter cases was attributed to exposure to poultry. The contractor concluded that enteritis due to Campylobacter is more common than that due to Salmonella, and that Campylobacter including resistant strains, appears to flow from chickens to man via contact with poultry products.

Holmberg, et al.

On August 24 of this year in the journal Science, Dr. Scott Holmberg and others at the Centers for Disease Control (CDC) reported on a retrospective analysis of outbreaks of human Salmonella infections in the United States. Fifty-two outbreaks of antibiotic-resistant Salmonella infections over a 13-year period were examined. The

researchers found that the fatality rate was much higher for persons with antibiotic-resistant infections than for persons with antibiotic-sensitive infections, and that food animals were a major source of antibiotic-resistant and antibiotic sensitive Salmonella strains. They concluded that antibiotic-resistant bacteria frequently originate from food animals and can cause serious infections in man. Another report by Dr. Holmberg and others at CDC appeared in the September 6 issue of the New England Journal of Medicine. This study received widespread attention earlier this year. Eighteen persons in four states had contracted Salmonella infections with multiple antibiotic resistance, and the researchers concluded that the bacteria originated from a beef herd that had received subtherapeutic antibiotics. The researchers concluded that antibiotic-resistant strains of bacteria of animal origin can cause serious human illness.

The Center currently is reviewing these data in addition to other information and data generated since 1977. Upon completion of our review and analysis, we will make a decision whether to go forward with the administrative proceeding in accordance with statutory requirements for the withdrawal of subtherapeutic uses of penicillin and the tetracyclines in animal feeds as described earlier.

PETITION--IMMINENT HAZARD TO THE PUBLIC HEALTH

On November 20 of this year, Secretary Heckler received from the Natural Resources Defense Council (NRDC) a petition to declare the subtherapeutic uses of penicillin and the tetracyclines in animal feeds an imminent hazard to the public health. NRDC argues that, on the

basis of three recently published scientific studies--the O'Brien and the two Holmberg studies discussed earlier--FDA is likely to eventually withdraw approval of the subtherapeutic uses of penicillin and the tetracyclines in animal feeds. NRDC argues, based on these studies, that these uses meet the criteria for imminent hazard under the law.

Before making any recommendation to FDA Commissioner Young and then to Secretary Heckler, I believe that the Center must evaluate all available information, and not just the three studies cited, before deciding on the petition. To assist in identifying pertinent available data and information, FDA has decided to hold a legislative-type hearing (21 CFR Part 15) in which interested persons are invited to present their views. This notice was published in the Federal Register. The criteria used to evaluate the petition will be:

-- The likelihood that FDA will eventually withdraw approval;
-- The severity of harm pending withdrawal of approval;
-- The likelihood of harm pending withdrawal of approval;
-- The risk to treated animals from suspended marketing; and
-- Other approaches to protect the public health.

After the legislative-type hearing, a recommendation on the petition will be formulated after the Center has completed its review of results from FDA contracts, the published literature, and other data and information, especially that brought to our attention at the hearing. Based on this review, the Agency will make a recommendation to the Secretary, who has nondelegable authority to declare drugs an imminent hazard.

If the Agency decides to proceed with withdrawal, a formal evidentiary public hearing before an administrative law judge (ALJ) would be required. Under our law, such a hearing would be needed in this case even if the drug uses in question were to be found an imminent hazard, and even if FDA holds a legislative-type hearing on the imminent hazard petition. Granting an imminent hazard petition does not avoid formal proceedings. Rather, granting a petition suspends the marketing of a drug immediately--before the completion of the formal evidentiary public hearing, the ALJ's initial decision, and the Commissioner's final decision. Under the ordinary withdrawal procedures, in which a drug does not meet statutory requirements but does not present an imminent hazard, the drug may be marketed until the completion of all of these steps.

CONCLUSION

At the time of our original proposal to ban the subtherapeutic uses of penicillin and the tetracyclines in animal feeds, the contention was advanced that there were gaps in the scientific position to supporting the chain of events linking low level antibiotic feedings to disease in humans. Since then, newly generated data have been useful in filling these gaps in our knowledge. After we review and evaluate these new data, the Agency will know whether to proceed with the proposed ban. From this review, along with a study of the information presented in the legislative-type hearing, the Agency will also be prepared to make a recommendation to the Secretary on NRDC's hazard petition.

In sum, two decisions must be made in the near future: first, whether to move forward with the withdrawal proceedings, and second, whether the hazards to human health are of such significance as to call for an immediate ban of low level uses of penicillin and the tetracyclines in animal feeds. Sometime in the spring we expect to recommend that the Secretary grant or deny the imminent hazard petition.

Mr. Chairman, this concludes my formal statement. I will be happy to answer any questions you or members of the Subcommittee might have.

SUBMISSIONS FOR THE RECORD

1. O'Brien, Thomas F., et al., 1982, "Molecular Epidemiology of Antibiotic Resistance in Salmonella from Animals and Human Beings in the United States," New England Journal of Medicine 307:1 pp. 1-6

2. "Surveillance of the Flow of Salmonella and Campylobacter in a Community," Communicable Disease Control Section, Seattle-King County Department of Public Health, Contract Number 223-81-7041

3. Holmberg, Scott D., et al., 1984, "Animal-to-Man Transmission of Antimicrobial-Resistant Salmonella: Investigations of U.S. Outbreaks, 1971-1983," Science, 225:4664, pp. 833-835

4. Holmberg, Scott D., et al. 1984, "Drug-Resistant Salmonella From Animals Fed Antimicrobials," New England Journal of Medicine, 311:10, pp. 617-621

5. Petition of the Natural Resources Defence Council, Inc. to the Secretary of Health and Human Services reguesting Immediate Suspension of Approval of the Subtherapeutic Use of Penicillin and Tetracyclines in Animal Feeds, November 20, 1984

Mr. GORE. Thank you very much. We'll hold off on questions, and we'll now hear from Dr. Donald Houston, Administrator of the Food Safety and Inspection Service at USDA. Dr. Houston, welcome, and please proceed.

[The biographical sketch of Dr. Houston follows:]

BIOGRAPHY

DONALD L. HOUSTON
Administrator
Food Safety and Inspection Service

Dr. Donald L. Houston was named administrator of the U.S. Department of Agriculture's Food Safety and Quality Service on July 14, 1979. He continued as Administrator of the Food Safety and Inspection Service (FSIS) when it was formed in June of 1981. Dr. Houston is responsible for the overall administration of FSIS which includes responsibility for conducting Federal meat and poultry inspection, the administration of the Humane Slaughter Act and the certification that State and foreign inspection systems meet U.S. requirements for meat and poultry products. He also holds the position of U.S. Coordinator and delegate to the Codex Alimentarius Commission.

Dr. Houston joined the Department in 1961 as a veterinary medical officer in the meat inspection program. He was assigned to the St. Louis, Missouri, inspection station until 1965, when he transferred to the headquarters staff in Washington, D.C. Since then he has held a number of technical and administrative positions of increasing responsibility related to food processing and food hygiene.

He is a member of the American Veterinary Medical Association and a Diplomate of the American College of Veterinary Preventive Medicine as well as other scientific and professional organizations.

Dr. Houston was born in East St. Louis, Illinois, on September 14, 1934. He is a 1959 graduate of the University of Illinois, Champaign, where he earned his doctorate in veterinary medicine. Following his university training, he served as an officer in the U.S. Army Veterinary Corps until he joined USDA. Dr. Houston is married, has one child, and resides in Arlington, Virginia.

Dr. HOUSTON. Thank you very much, Mr. Chairman.

Like Dr. Crawford, I am pleased to have the opportunity to appear before the subcommittee today and discuss the Department of Agriculture's program for detecting residues of antibiotics in food-producing animals.

FSIS, of the Department of Agriculture, is responsible for enforcing the Federal Meat Inspection Act and the Poultry Products Inspection Act. In carrying out this responsibility, the agency operates a national residue program to detect and prevent the occurrence of potentially harmful residues of drugs, including antibiotics and other chemicals in meat and poultry products.

The agency collects samples of meat and poultry from official slaughtering establishments and from imported shipments at ports of entry. The samples are analyzed to detect the presence of illegal residues of pesticides, animal drugs and other potentially hazardous chemicals that may adulterate meat and poultry.

FSIS carries out its residue control responsibilities in cooperation with other Federal agencies. For the most part, these efforts are coordinated among FSIS, FDA, and the Environmental Protection Agency. With respect to animal drugs, FSIS cooperates with the Food and Drug Administration in preventing food from entering commerce that has been contaminated with illegal drug residues.

FDA enforces regulations for the approval of new animal drug applications and the establishment of residue tolerances and withdrawal periods for drugs or medicated feed used in food-producing animals. The Meat and Poultry Inspection Acts provide for the condemnation of carcasses found to contain illegal drug residues which adulterate those carcasses.

The USDA National Residue Program began in 1967 with the original purpose of learning the effect of pesticide contamination on food animals.

Mr. GORE. Excuse me, Dr. Houston.

Dr. HOUSTON. Yes, sir.

Mr. GORE. I don't see anything in your statement about the issue that we're—about the issue that we're looking at here. Is this whole statement about your procedures for inspecting for residue?

Dr. HOUSTON. Yes, sir; it is. That was the agreement we came to with the staff.

Mr. GORE. Does the USDA have a position on the—on this issue that we're looking at here today?

Dr. HOUSTON. No, sir; we do not.

Mr. GORE. OK. Well, if it won't hurt your feelings, I'd like to put this in the record——

Dr. HOUSTON. That'll be fine.

Mr. GORE [continuing]. The statement of—of your inspections of residues and I do appreciate it very much.

[The prepared statement of Dr. Houston follows:]

STATEMENT BY:

DR. DONALD L. HOUSTON, ADMINISTRATOR
FOOD SAFETY AND INSPECTION SERVICE
UNITED STATES DEPARTMENT OF AGRICULTURE

BEFORE:

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE AND TECHNOLOGY
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

DECEMBER 18, 1984

GOOD MORNING, MR. CHAIRMAN. I AM PLEASED TO HAVE THE OPPORTUNITY TO APPEAR BEFORE YOU TODAY TO DISCUSS THE DEPARTMENT OF AGRICULTURE'S PROGRAM FOR DETECTING RESIDUES OF ANTIBIOTICS IN FOOD-PRODUCING ANIMALS.

THE FOOD SAFETY AND INSPECTION SERVICE (FSIS) OF THE DEPARTMENT OF AGRICULTURE (USDA) IS RESPONSIBLE FOR ENFORCING THE FEDERAL MEAT INSPECTION ACT AND THE POULTRY PRODUCTS INSPECTION ACT. THE PRINCIPAL PURPOSE OF THESE LAWS IS TO ENSURE THAT MEAT AND POULTRY PRODUCTS DISTRIBUTED TO CONSUMERS ARE WHOLESOME, NOT ADULTERATED, AND PROPERLY MARKED, LABELED, AND PACKAGED. IN CARRYING OUT THIS RESPONSIBILITY, THE AGENCY OPERATES A NATIONAL RESIDUE PROGRAM TO DETECT AND PREVENT THE OCCURRENCE OF POTENTIALLY HARMFUL RESIDUES OF DRUGS--INCLUDING ANTIBIOTICS--AND OTHER CHEMICALS IN MEAT AND POULTRY PRODUCTS. THE AGENCY COLLECTS SAMPLES OF MEAT AND POULTRY FROM OFFICIAL SLAUGHTERING ESTABLISHMENTS AND FROM IMPORTED SHIPMENTS AT PORTS OF ENTRY. THE SAMPLES ARE ANALYZED TO DETECT THE PRESENCE OF ILLEGAL RESIDUES OF PESTICIDES, ANIMAL DRUGS, AND OTHER POTENTIALLY HAZARDOUS CHEMICALS THAT MAY ADULTERATE MEAT AND POULTRY.

FSIS CARRIES OUT ITS RESIDUE CONTROL RESPONSIBILITIES IN COOPERATION WITH OTHER FEDERAL AGENCIES. FOR THE MOST PART, THESE EFFORTS ARE COORDINATED AMONG FSIS, FDA, AND THE ENVIRONMENTAL PROTECTION AGENCY. WITH RESPECT TO ANIMAL DRUGS, FSIS COOPERATES WITH THE FOOD AND DRUG ADMINISTRATION (FDA) IN PREVENTING FOOD FROM ENTERING COMMERCE THAT HAS BEEN CONTAMINATED WITH ILLEGAL DRUG RESIDUES. FDA ENFORCES REGULATIONS FOR THE APPROVAL OF NEW ANIMAL DRUG APPLICATIONS AND THE ESTABLISHMENT OF RESIDUE TOLERANCES AND WITHDRAWAL PERIODS FOR DRUGS OR MEDICATED FEED USED IN FOOD-PRODUCING ANIMALS. THE MEAT AND POULTRY INSPECTION ACTS PROVIDE FOR THE CONDEMNATION OF CARCASSES FOUND TO CONTAIN ILLEGAL DRUG RESIDUES WHICH ADULTERATE THE CARCASS.

THE USDA NATIONAL RESIDUE PROGRAM BEGAN IN 1967 WITH THE ORIGINAL PURPOSE OF LEARNING THE EFFECT OF PESTICIDE CONTAMINATION ON FOOD ANIMALS. SINCE THEN, THE PROGRAM HAS EVOLVED INTO A SYSTEMATIC, NATIONWIDE OPERATION THAT MONITORS FOR A LARGE NUMBER OF DRUG AND OTHER CHEMICAL RESIDUES. THE PROGRAM IS MANAGED BY A MULTIDISCIPLINARY TEAM OF SCIENTISTS. IT HAS TWO ASPECTS, ONE REGULATORY AND ONE NON-REGULATORY.

THE REGULATORY FUNCTION INCLUDES MONITORING AND SURVEILLANCE PHASES. IN THE MONITORING PHASE, INSPECTORS TAKE TISSUE SAMPLES FROM RANDOMLY SELECTED CARCASSES AT SLAUGHTERING PLANTS AND IMPORT INSPECTION FACILITIES AROUND THE COUNTRY. FROM THE MORE THAN 210,000 TESTS CONDUCTED ON THE 28,000 DOMESTIC SAMPLES COLLECTED ANNUALLY, FSIS DETERMINES RESIDUE INCIDENCE AND TRENDS AND IDENTIFIES SPECIFIC PROBLEMS.

IN THE SURVEILLANCE PHASE, FSIS TESTS TISSUES FROM SPECIFIED SUSPECT ANIMALS. FOR EXAMPLE, TESTING IN THIS PHASE IS INITIATED AFTER INFORMATION DEVELOPED THROUGH THE MONITORING PROGRAM INDICATES A PROBLEM THAT DESERVES INTENSIFIED TESTING OF LIVESTOCK OR POULTRY FROM A FARM OR GEOGRAPHIC AREA. ONCE VIOLATIONS ARE DETECTED, IT IS OUR POLICY TO WITHHOLD FURTHER CARCASSES FROM THE FOOD SUPPLY UNTIL LABORATORY TESTING SHOWS THAT A VIOLATIVE RESIDUE LEVEL IS NOT PRESENT.

INFORMATION ON VIOLATIONS GATHERED FROM ANY PHASE OF THE PROGRAM IS REFERRED TO FDA OR EPA FOR THEIR REVIEW AND USE IN CONDUCTING INVESTIGATIONS TO DETERMINE IF CHEMICALS WERE MISUSED. A FLAGRANT VIOLATION OF THE LAW OR REPEATED MISUSE CAN RESULT IN THE CRIMINAL PROSECUTION OF PRODUCERS.

UNDER THE FEDERAL MEAT AND POULTRY INSPECTION ACTS, FOREIGN COUNTRIES THAT EXPORT MEAT AND POULTRY OR PRODUCTS THEREOF TO THE UNITED STATES ARE REQUIRED TO MAINTAIN INSPECTION SYSTEMS THAT COMPLY WITH LAWS THAT ARE AT LEAST EQUAL TO THE PROVISIONS OF THE FEDERAL MEAT AND POULTRY INSPECTION ACTS AND REGULATIONS THEREUNDER. THIS INCLUDES THE REQUIREMENT FOR A RESIDUE CONTROL PROGRAM AT LEAST EQUAL TO THAT IN THE UNITED STATES. IF A SAMPLE OF IMPORTED PRODUCT FAILS A RESIDUE TEST UNDER OUR MONITORING PROGRAM, THE SAMPLING RATE IS DOUBLED FOR THE FAILING PRODUCT AND RELATED PRODUCTS FROM THE SAME COUNTRY. FURTHER SHIPMENTS OF THE SAME OR RELATED PRODUCTS FROM THE FOREIGN PLANT INVOLVED IN THE FAILURE ARE PLACED UNDER A SURVEILLANCE SAMPLING PROGRAM. THE SURVEILLANCE PROGRAM REMAINS IN EFFECT UNTIL AT LEAST 15 CONSECUTIVE SAMPLES OF PRODUCT FROM THE ESTABLISHMENT HAVE PASSED RESIDUE TESTS. WHEN FSIS IS SATISFIED THAT THE PROBLEM HAS BEEN RESOLVED, NORMAL PROCEDURES CAN BE RESUMED. IN THE CASE OF ANTIBIOTICS, HOWEVER, WE HAVE NOT BEEN FINDING ANY RESIDUE PROBLEMS WITH FOREIGN PRODUCTS. FOR EXAMPLE, IN 1983 WE FOUND NO VIOLATIONS FOR ANTIBIOTIC RESIDUES IN IMPORTED MEAT AND POULTRY PRODUCTS. SO FAR IN 1984 WE HAVE ALSO FOUND NO VIOLATIONS.

THE NONREGULATORY ASPECTS OF THE NATIONAL RESIDUE PROGRAM INCLUDE THE RESIDUE AVOIDANCE PROGRAM AND EXPLORATORY EFFORTS. THE RESIDUE AVOIDANCE PROGRAM IS A COOPERATIVE EFFORT AMONG VARIOUS AGENCIES OF THE U.S. DEPARTMENT OF AGRICULTURE, THE FOOD AND DRUG ADMINISTRATION, AND PRODUCER ORGANIZATIONS. THE PURPOSE OF THIS PROGRAM IS TO HELP FARMERS AND OTHERS INVOLVED IN ANIMAL PRODUCTION TO REDUCE THE POTENTIAL FOR ACCIDENTAL RESIDUE PROBLEMS. THE PROGRAM, ADMINISTERED THROUGH THE EXTENSION SERVICE, IS DESIGNED TO ASSIST PRODUCERS IN IDENTIFYING

POINTS IN THEIR PRODUCTION SYSTEMS WHERE ANIMALS MIGHT BECOME CONTAMINATED. THROUGH CAREFULLY PLANNED PREVENTIVE ACTION TAKEN AT THESE POINTS, RESIDUE VIOLATIONS WILL BECOME LESS LIKELY.

UNDER THE EXPLORATORY PHASE, FSIS CAN COLLECT SAMPLES FROM A VARIETY OF ANIMAL SPECIES AND TEST THEM FOR A PARTICULAR CONTAMINANT, SUCH AS A WOOD PRESERVATIVE, INDUSTRIAL CHEMICAL, OR AN UNAPPROVED DRUG OR FEED ADDITIVE, TO SEE IF A RESIDUE PROBLEM EXISTS AND WHETHER REGULATORY EFFORTS NEED TO BE MADE.

BECAUSE OF THE DIVERSITY OF SUBSTANCES THAT MAY THEORETICALLY OCCUR AS RESIDUES IN MEAT AND POULTRY, FSIS USES A SYSTEM OF EVALUATING COMPOUNDS FOR THEIR POTENTIAL TO CAUSE ADULTERATING RESIDUES AND ASSIGNS THEM A PRIORITY CLASSIFICATION FOR MONITORING. A SURVEILLANCE ADVISORY TEAM, INCLUDING SCIENTISTS FROM EPA AND FDA, ASSISTS FSIS IN THE EVALUATION AND SELECTION OF COMPOUNDS FOR MONITORING. THE SURVEILLANCE ADVISORY TEAM MEETS TWICE YEARLY. FSIS ALSO PARTICIPATES WITH FDA IN THE EVALUATION OF RESIDUE ANALYTICAL PROCEDURES SUBMITTED TO FDA WITH EACH NEW ANIMAL DRUG APPLICATION.

ANTIBIOTIC RESIDUE PROBLEMS

SINCE OUR MONITORING PROGRAM HAS BEEN IN EXISTENCE, WE HAVE FOUND THAT THE OVERALL INCIDENCE OF VIOLATIVE ANTIBIOTIC RESIDUES IN BOTH DOMESTIC AND IMPORTED MEAT PRODUCTS HAS BEEN LOW. FOR EXAMPLE, IN 1983, IN SUCH WIDELY CONSUMED SPECIES AS YOUNG CHICKENS AND STEERS, WE RECORDED NO ANTIBIOTIC RESIDUE VIOLATIONS IN OUR MONITORING PROGRAM. MOREOVER, THE LOW-LEVEL, OR SUBTHERAPEUTIC, USE OF ANTIBIOTICS IN ANIMAL FEED HAS NOT BEEN SHOWN TO CAUSE

RESIDUE PROBLEMS. IN GENERAL, THE ANTIBIOTIC RESIDUE PROBLEMS WE HAVE ENCOUNTERED INVOLVED THE MISUSE OF ANTIBIOTICS IN TREATMENT SITUATIONS--MOSTLY IN CULL DAIRY COWS AND DAIRY CALVES SENT TO SLAUGHTER A FEW DAYS AFTER BIRTH.

TO DEAL WITH THIS SITUATION, USDA CARRIED OUT A VIGOROUS PRODUCER EDUCATION EFFORT THROUGH THE EXTENSION SERVICE AND IN COOPERATION WITH PRODUCER ORGANIZATIONS. ALSO, OUR MICROBIOLOGY STAFF DEVELOPED A NEW SCREENING TEST TO DETECT ANTIBIOTIC RESIDUES IN ANIMAL KIDNEYS AND MUSCLE TISSUE. THE SCREENING TEST, WHICH WAS IMPLEMENTED IN 1979, IS CALLED STOP--FOR SWAB TEST ON PREMISES. BEFORE STOP WAS IMPLEMENTED, SUSPECT CARCASSES HAD TO BE RETAINED UNTIL TISSUE SAMPLE RESULTS COULD BE OBTAINED FROM USDA LABORATORIES. STOP, HOWEVER, PERMITS INSPECTION PERSONNEL TO DETERMINE QUICKLY IF THE SUSPECT PRODUCT CAN BE PASSED AND RELEASED, OR IF IT MUST BE RETAINED FOR ADDITIONAL TESTING.

FOLLOWING ANTEMORTEM AND POSTMORTEM INSPECTION, FSIS INSPECTORS USE THE STOP TEST ON CARCASSES OF ANIMALS SHOWING INJECTION LESIONS OR ANIMALS SUSPECTED OF RECEIVING ANTIBIOTIC TREATMENT FOR DISEASE. TO PERFORM THE TEST, A COTTON SWAB IS INSERTED INTO ANIMAL TISSUE WHERE IT BECOMES SATURATED WITH TISSUE FLUID. THEN THE SWAB IS PUT ON A CULTURE PLATE SEEDED WITH HARMLESS ORGANISMS. IF ANTIBIOTICS ARE IN THE TISSUE FLUID, ORGANISMS WILL NOT GROW NEAR THE SWAB--SO A CLEAR INHIBITION ZONE IS LEFT AROUND THE SWAB.

THE STOP TEST IS USUALLY COMPLETED IN 18 HOURS. IF THE SAMPLE IS POSITIVE, THE CARCASS IS RETAINED AT THE PLANT WHILE KIDNEY AND MUSCLE SAMPLES UNDERGO FURTHER TESTS IN AN FSIS LABORATORY TO DETERMINE THE SPECIFIC ANTIBIOTIC PRESENT AND ITS LEVEL OF CONCENTRATION. IF THE STOP TEST IS NEGATIVE, THE CARCASS CAN BE RELEASED.

STOP HAS ENABLED THE AGENCY TO TEST MORE SUSPECT COWS WITH FASTER RESULTS. PACKERS ARE ABLE TO LEARN QUICKLY WHICH PRODUCERS OR DEALERS ARE MARKETING VIOLATIVE COWS. IMPLEMENTATION OF STOP LED TO A DRAMATIC REDUCTION IN VIOLATIONS. SINCE 1981, THE ANNUAL RATE HAS BEEN LESS THAN 1 PERCENT OF ALL COWS TESTED. DAIRYMEN WHO SEND CULL COWS TO SLAUGHTER WITH VIOLATIVE LEVELS HAVE LEARNED THE HIGH RISK THEY RUN OF BEING DETECTED.

THIS YEAR, ON JUNE 7, WE PUBLISHED AN EMERGENCY INTERIM RULE ANNOUNCING A NEW INPLANT TESTING PROGRAM FOR DETECTING VIOLATIVE RESIDUES IN NEWBORN CALVES. THE INPLANT TEST USED IN CARRYING OUT THE REGULATION IS CALLED CAST--FOR CALF ANTIBIOTIC SULFA TEST. THE TEST IS BASED ON THE SAME PRINCIPLE AS THE STOP TEST. HOWEVER, THIS IS AN EVEN MORE ADVANCED TEST. RESULTS OF CAST DETERMINE THE DISPOSITION OF THE CARCASS WITHOUT ANY FURTHER LABORATORY ANALYSIS. ALTHOUGH IT IS TOO EARLY TO JUDGE THE PERMANENT IMPACT OF THE NEW RULES AND THE CAST TEST, I AM CONFIDENT THAT THIS ENHANCED REGULATORY EFFORT WILL PROVE TO BE VERY EFFECTIVE. WE HAVE SOLID SUPPORT FROM THE AFFECTED PACKERS AND PRODUCERS. THE OVERWHELMING MAJORITY OF COMMENTS WE HAVE RECEIVED HAVE SUPPORTED STRICT ENFORCEMENT OF THE REGULATION AS WRITTEN.

CONCLUSION

IN THE LAST THREE YEARS OUR RESIDUE PROGRAM HAS SHIFTED FROM A REACTIVE ORIENTATION TO A PROACTIVE, PREVENTIVE ONE. WE HAVE SOUGHT TO INVOLVE PRODUCERS MORE ACTIVELY IN KEEPING THE FOOD SUPPLY FREE OF POTENTIALLY HARMFUL RESIDUES BEFORE THEY BECOME PROBLEMS FOR THE INSPECTION SERVICE OR CONSUMERS. AT THE SAME TIME, WE HAVE IMPROVED OUR ENFORCEMENT--BOTH IN THE DESIGN OF OUR PROGRAM AND IN THE CAPABILITY OF OUR TESTING. THE EMERGENCE OF THE NEW, QUICK TESTS IMPROVES OUR ENFORCEMENT ABILITY AND HOLDS THE PROMISE OF ENABLING PRODUCERS TO BETTER FULFIL THEIR ROLE IN RESIDUE PREVENTION. IN OUR EXPERIENCE, THE COMBINATION OF RESIDUE MONITORING AND PRODUCER EDUCATION IS WORKABLE, AND ULTIMATELY WILL PROVE EFFECTIVE IN KEEPING POTENTIALLY HARMFUL RESIDUES OUT OF THE FOOD SUPPLY.

Mr. GORE. And I believe I understand why USDA is reluctant to get involved in this. I think probably you should because of your expertise, but I understand the political pressures that are brought to bear. Believe me, I do.

Dr. HOUSTON. We look forward to seeing what transpires after the hearing in January.

Mr. GORE. Yes, all right. Well, maybe we can get your help on some of these questions, nonetheless——

Dr. HOUSTON. Fine.

Mr. GORE [continuing]. Here today.

Dr. Crawford—and I don't wish to be impolite on—on interrupting your reading of the statement—I hope that's all right——

Dr. HOUSTON. Perfectly fine.

Mr. GORE. All right, fine.

Dr. Crawford, is it correct that FDA's 1977 proposal to ban penicillin and restrict tetracycline in animal feeds covered only subtherapeutic and not therapeutic uses?

Dr. CRAWFORD. That's right. With respect to penicillin, those orders, in effect, Mr. Chairman, banned all uses of penicillin in animal feed. However, they had no effect on the uses of penicillin for other purposes in veterinary or human services, but penicillin would have been taken out of animal feed.

The restrictions on tetracycline were much less broad. Only some uses of tetracycline would be affected. Generally those very low level uses that only have to do with the improvement of growth and feed efficiency, such as Dr. Hays mentioned. Uses of tetracycline that were considered essential, particularly those for which there was no substitute, would not be affected.

Also, like penicillin, we propose not to affect the use of tetracycline as an injectable, as a water-soluble product, or in any other form. It would just be the animal feed uses and not nearly all of them.

Mr. GORE. And what's under consideration now at FDA is also limited to subtherapeutic uses of these two drugs; is that correct?

Dr. CRAWFORD. We haven't changed the position since 1977——

Mr. GORE. Yeah.

Dr. CRAWFORD [continuing]. And in effect, those orders are still in effect. They're in abeyance, however.

Mr. GORE. Yes.

If subtherapeutic uses should be restricted, but therapeutic uses still permitted, how can you assure that such an outcome would, in fact, reduce the level of resistance in bacteria?

Dr. CRAWFORD. Well, we can't be sure about that because, as was mentioned in the other panel, antibiotic resistance appears to be a great ecosystem involving all uses and involving both man and animals and resistance appears to flow from one to the other.

Our lessons in this regard mainly come from what has happened in other countries. It was mentioned that in England that—I believe Dr. Sabath said not much had changed in terms of the resistance patterns because of the efforts they initiated in 1970 and 1971 under the Swann report. However, what we found in England is that these products were put on prescription and then over time, they appear to be used at about the same level as they were prior to the restrictions.

Mr. GORE. So my statement earlier was correct, in your opinion, that their ban in England really hasn't been effective because the practices have continued just as they were before the ban. And didn't, in fact, some English—there was testimony at one of the—at the NIH conference or—where was that testimony from the English—there was testimony recently from some people from England about this subject saying that it really hadn't had much effect because of the way it was carried out. They're still using it in just the same quantities as they were before.

Dr. CRAWFORD. There is a wide variety of views about what the British did. One conclusion I think all people adopt, and that is, that what they did did not work. Now, in other countries—for instance, in Holland, where some restrictions were placed on tetracycline—improvements did occur in the susceptibility patterns of bacteria and this has been true elsewhere.

Dr. Hays, in the earlier panel, mentioned that when he began restricting the use of tetracyclines, 90 percent of the pathogens available on the farm at the University of Kentucky were resistant to tetracycline and after some 12 years of that abolition, self-imposed, that now between 20 and 50 percent of isolates are resistant to tetracycline, and that's about what most people expect will happen.

Most authorities that we're in communication with believe that you're not going to affect a complete cure, particularly with the small steps that FDA has proposed, but that there will be some improvement.

Mr. GORE. It's true that most veterinary drugs, including antibiotics, are available as over-the-counter drugs to livestock producers. That is, they're available in the feed store. I know that I have a close involvement with a feed store in my hometown in Carthage, TN, and it's just—they're just widely available. Just go and buy them with no problem.

FDA has no plans to change that kind of policy for antibiotic use in animals; is that correct?

Dr. CRAWFORD. That's right. The way the law is written in terms of applying to veterinary drugs, essentially when we consider a drug for approval, it is over the counter unless it's an unusual sort of product. The language we use to describe the other type of product, which is prescription, is that if adequate directions cannot be written for lay use, or use by a nonveterinarian, the product has to be prescription. Most drugs that are approved are approved over the counter, including penicillin and tetracycline, the injectible preparations, the feed preparations, and all the other forms, are at least in some form over the counter. Most veterinary drugs for large animal use—that is, for farm animal use—are over the counter. Most for small animal use, or pet animal use, are prescription.

Mr. GORE. Now, they're not over the counter in England, right?

Dr. CRAWFORD. Well, some are and some aren't. In the United Kingdom, the penicillin and tetracycline that are added to feed may be added only with the prescription.

Mr. GORE. OK, now, but the pattern that is reported to have taken place in England——

Dr. CRAWFORD. Uh-huh.

Mr. GORE [continuing]. Is since the ban is additives there——

Dr. CRAWFORD. Uh-huh.

Mr. GORE [continuing]. Is that the number of prescriptions by veterinarians has just skyrocketed——

Dr. CRAWFORD. Uh-huh.

Mr. GORE [continuing]. And the presumption is that farmers are just getting the antibiotics from their vets and adding it on their own. Now, if these antibiotics are available over the counter without a prescription here in the United States, and if the kind of ban that you're considering was put into effect, why wouldn't you expect the economic pressures that come from the advantages from using subtherapeutic doses of antibiotics, why wouldn't you expect those economic pressures to lead to an increase in the purchases of over-the-counter products by farmers and an adding of those to their feed on their own?

Dr. CRAWFORD. Well, the FDA orders of 1977 would, in the case of penicillin, for instance, make it illegal in the United States to add that to animal feed. Now, other forms of penicillin could be bought and used for veterinary purposes, the injectable, for instance. No one could add it to animal feed under any circumstances, so we would be sure that that practice would not take place anymore were we to affect——

Mr. GORE. How would you be sure that the farmer wouldn't add it himself?

Dr. CRAWFORD. Well, it would not be available in any preparation that could be added to animal feed.

Mr. GORE. OK.

Dr. CRAWFORD. If such a preparation would be detected by our surveillance system, our enforcement people, then it would be seized because the mere existence of such a product would be illegal.

Mr. GORE. I see. All right.

How—how widespread is the resistance problem in animals or is it growing, and is FDA aware of any problems that veterinarians have with drug-resistant bacteria?

Dr. CRAWFORD. Well, since the introduction of the antibiotic era in veterinary medicine which occurred in human medicine at about the same time as in human medicine—late 1940's and early 1950's, these products have declined in effectiveness.

Dr. Sabath showed some charts which indicated that the level of resistance has stabilized to some extent in the last few years. I believe some of his charts, however, showed 100 percent resistance, and one would expect that to stabilize. However, others flatten out at less than that. But if you were to take, say, a segment of time from 1955 to 1985, you would see that antibiotics in veterinary medicine that were being marketed in 1955 had declined to some extent in effectiveness since that time.

Mr. GORE. I see. Now, for what reasons were the proposed restrictions limited to penicillin and tetracycline?

Dr. CRAWFORD. I was not at FDA at that time, but I believe the rationale was that these are very important for therapy of human diseases, whereas the others that are added to animal feed and approved by FDA are not as important in the therapy of human diseases. So they picked out penicillin and tetracycline.

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The policy decision was made in 1973 at FDA that so-called human-use antibiotics would no longer be added to animal feed as a matter of policy. But in 1973, penicillin and tetracycline were already approved, so the decision not to add the new generation of human-use antibiotics to animal feed triggered an examination of penicillin and tetracycline.

It was felt that——

Mr. GORE. I see.

Dr. CRAWFORD [continuing]. They should be given due process. They should be——

Mr. GORE. Yeah.

Dr. CRAWFORD [continuing]. Looked at carefully because they may be vital to animal agriculture.

Mr. GORE. Yeah.

Why was penicillin treated more stringently than tetracycline?

Dr. CRAWFORD. Well, penicillin is—in the view of most people, still a very essential antibiotic for human therapy and veterinary therapy. Many cases—some of the natural penicillins, the semi-synthetics and the new generations of synthetics that Dr. Sabath alluded to are among the most effective and most widely used antibiotics for serious human disease, and it was felt that, on an order of magnitude, penicillin was——

Mr. GORE. It's more important——

Dr. CRAWFORD [continuing]. More important.

Mr. GORE [continuing]. Than tetracycline.

Dr. CRAWFORD. Uh-huh.

Mr. GORE. All right.

Dr. Houston, although your statement goes into the question of residues, there are bacteria also in the jurisdiction of USDA and I want to ask you a few questions about them.

To what extent are pathogenic bacteria legally permitted to occur in meat that's found in supermarkets?

Dr. HOUSTON. Well, let's break that into two parts, if we may. First of all, our policy on pathogens in any product that is cooked and ready to eat or maybe have to be just heated before eating—in those cases, they are considered adulterants and we would take action to remove that product from the marketplace, such as a pre-cooked roast beef item, as one example, or a heat-and-serve dinner.

Mr. GORE. Yeah.

Dr. HOUSTON. In raw meat, we do not consider Salmonella, as an example, a pathogen or an—excuse me, an adulterant. It is a pathogen, but the food is not considered adulterated because of, quite frankly, the large amount of Salmonella that is in our food supply today and has been there for a number of years.

In 1971, the—and I might say that that issue was decided in the courts in 1971 when the American Public Health Association sued the Department, suggesting in their suit that this—any food—meat or poultry, raw meat or poultry, containing Salmonella should be considered adulterated and moved—removed from the marketplace or be labeled as "Dangerous, may contain Salmonella," or some kind of warning labeling.

The courts found that that wasn't necessary and that the normal prudent practices that one needs to take in preparing raw meat and poultry were sufficient to protect against food poisoning. At

that time, the Department also, in agreement with the court, undertook an extensive food safety program and has spent literally millions of dollars in that area over the last several years.

I do have data here if you're interested in incidence of Salmonella in meat and poultry.

Mr. GORE. Yeah, why don't you share that briefly. We'll put the more extensive version in the record.

[The information follows:]

PERCENT INCIDENCE OF SALMONELLA IN MEAT AND POULTRY

FSIS

NATIONAL SURVEYS

PRODUCT	YEAR	PERCENT
Pork; Fresh Pork Sausage	1969	28.6
Pork; Fresh Pork Sausage	1979	12.4
Chicken; Broilers	1967	28.6
Chicken; Broilers	1979	36.9
Chicken; Broilers	1982-84	35.0
Beef; Ground Beef	1971-73	0.4
Turkey; Semi-seasonal, Not Done		

Dr. HOUSTON. Right, just a couple of examples. In 1969, our survey on fresh pork sausage showed a 28-percent incidence. In 1979, it had dropped to 12.4 percent, so we saw some improvement there.

In 1967, our data on broilers was 28 percent and in 1979, had risen to almost 37 percent, and our latest survey, which was last year, was 35 percent.

We did a 3-year survey on ground beef back in 1971 and we saw an incidence of 0.4 percent.

Mr. GORE. What was that last?

Dr. HOUSTON. 0.4 percent.

Mr. GORE. For what?

Dr. HOUSTON. Ground beef and beef.

Mr. GORE. Yeah. So in your latest study for chickens, 38 percent contained——

Dr. HOUSTON. Thirty-five.

Mr. GORE. Thirty-five percent contained what now?

Dr. HOUSTON. We were able to——

Mr. GORE. Salmonella.

Dr. HOUSTON [continuing]. Isolate Salmonella. Those were whole-bird washings. We were able to isolate Salmonella from the bird in 35 percent of the cases.

Mr. GORE. OK. And you don't have legal authority to deal with that?

Dr. HOUSTON. We do have authority to take actions to minimize the opportunity for Salmonella contamination, but we do not take the position that those birds are adulterated and should be removed from the marketplace.

Mr. GORE. Because the normal cooking would render them——

Dr. HOUSTON. That's right, and——

Mr. GORE [continuing]. Harmless.

Dr. HOUSTON [continuing]. I would like to add that in New Orleans this year in July, there was an international symposium on Salmonella at which time about 200 of the world's leading experts on that problem came together to share information and at the end of the symposium, they came together in terms of consensus on 5 statements. I won't read them all, but one of them was that it should be candidly recognized that raw foods of animal origin are frequently contaminated by Salmonella and that such contamination levels cannot be expected to change greatly in the near future.

That, of course, is an outgrowth of how we slaughter, dress, and eviscerate animals in the meat industry.

Mr. GORE. Uh-huh. Well, my next question was going to be how come one out of four chickens in the Seattle-King County had bacteria, but I can see from your figures that they have a reduced incidence——

Dr. HOUSTON. They're talking there about—I was talking about Salmonella and I think they were talking about Campylobacter.

Mr. GORE. Oh, I see. All right, all right. Well, the figures that they're using are not—are they out of line there with——

Dr. HOUSTON. No, no, they're not.

Mr. GORE. All right.

Are allowable levels of penicillin in meat—and here I'm talking about residues—set in recognition of the fact that some individuals can suffer severe allergic reactions to those residues? Is that the reasoning behind——

Dr. HOUSTON. I'll defer to Dr. Crawford, since he's the one who sets those levels. We simply enforce them, but all of the tolerances and the withdrawal periods are set by FDA in their review of drug applications.

Dr. CRAWFORD. Yeah, those are set in recognition of that. What we attempt to do in setting a tolerance is setting a no-effect level. If a product, as you know, Mr. Chairman, is not a carcinogen, we're allowed to do that.

Mr. GORE. Yeah.

Dr. CRAWFORD. With penicillin, we set a level and then monitor for that level, where we don't expect that there will be any public health impact at all.

Mr. GORE. OK. So this allergic reaction problem is the one you're sensitive to?

Dr. CRAWFORD. Yes.

Mr. GORE. How frequent are reactions to penicillin residues?

Dr. HOUSTON. Well—from the food supply?

Mr. GORE. Yes.

Dr. HOUSTON. I think they're quite rare, but there are some on record. I recall one being reported this year in which an individual suffered a penicillin reaction after eating a meat product and we did get that index sample and we did find evidence of penicillin in that particular food and it's likely or possible that that individual did have that penicillin reaction from eating that particular meat food product. But that's the only one I'm aware of.

Mr. GORE. OK.

Mr. Volkmer.

Mr. VOLKMER. Dr. Crawford, before—or during the decision of FDA to either proceed or not proceed on recommendations to the Secretary, do you believe that any further studies, as recommended by the National Academy of Sciences, should be done?

Dr. CRAWFORD. I don't think it would be proper to comment on that until we decide this imminent hazard situation.

Mr. VOLKMER. Well, were all the studies done that they had recommended?

Dr. CRAWFORD. They were all addressed in one form or another. What we're doing now, Mr. Volkmer, as you know in all probability, is we're preparing a report to the Congress in which we address the NAS recommendations, tell what we did with the resources that we had to do them, and how we believe that we have satisfied the categories that they had suggested.

We had to take the recommendations that they put forward and analyze what we had ongoing at the present time. We had some studies under way at that time, such as Dr. O'Brien's study that he mentioned earlier today, and also we had to analyze what it was that we could do with the resources we had.

We believe we'll be able to address the issues that they raised, but that will await completion of that report which I can submit for the record here.

Mr. VOLKMER. Now, as I understand your testimony and I suppose that—I have no reason to disagree with you on it—that the practice in England has been, actually then, to continue the subtherapeutic use of antibiotics, even though theoretically prohibited?

Dr. CRAWFORD. They put them on prescription, which allowed veterinarians to prescribe their use. We also—you'll be interested to know—proposed that as a possibility in dealing with our problem here in 1978, and that was not received with much enthusiasm by our respondents that commented on that petition.

Most felt that it wouldn't do very much good. Others felt that it was unworkable because not enough veterinarians were involved throughout the country in dealing with the use of animal feed additives. Others thought there would be a great deal of paperwork and would be more trouble than the problem it was trying to solve.

So we put that proposal, which was the third of the three orders that we put forward in 1977 and 1978 on this issue, in abeyance because it was not considered to be something that would be worthwhile.

Mr. VOLKMER. Now, the prohibition that is proposed as far as penicillin, would that be applicable also to tetracycline?

Dr. CRAWFORD. No. The tetracycline proposals were limited in scope and we did not address—we exempted many of the uses of

tetracycline that are now approved. We addressed, for the most part, only those low-level uses that have to do with the growth promotion and feed efficiency.

Many uses of tetracycline would still be allowed, especially those for which we didn't see a substitute product on the market.

Mr. VOLKMER. All right. Are there any substitute products on the market presently being used on the subtherapeutic usage, either for animal growth even?

Dr. CRAWFORD. Yes, sir; there are other products that are approved for animal growth that, as far as FDA is concerned through its approval process, would be substitutes. Now, some authorities believe that these are not as effective as the other products; other authorities believe they're more effective. That's a question that FDA doesn't get into; basically on a scale of 1 to 10, which is the most effective.

To answer your question, there are substitutes available.

Mr. VOLKMER. Are there any other antibiotics that FDA is looking at on this question of resistance—bacteria resistance?

Dr. CRAWFORD. Well, we have to maintain surveillance of antibiotic resistance as it occurs in the United States. We have no other antibiotics under the kind of consideration in which we've placed penicillin and tetracycline in 1977. There are no more of these kinds of events being planned.

Mr. VOLKMER. So there could be other antibiotics used in animals, continuation and——

Dr. CRAWFORD. Yes, sir.

Mr. VOLKMER. Have there been any studies made as to the effect of the resistance levels on bacteria? The result of those antibiotics?

Dr. CRAWFORD. Yes; Dr. Sabath mentioned a book which was published in 1982 on this subject which tends to categorize the various ones of them. It points out that in several instances, the substitute antibiotics are not known to have a resistance problem. They would be essentially resistance free.

There's also another book that's come out that's about the same kind of discourse on the substitutes and also on the antibiotic resistance problem in general that was published in this country.

So there are a large number of studies. There are also studies comparing the relative effectiveness of the various range of antibiotics that are approved at the present time.

Mr. GORE. Would the gentleman yield on that question?

Mr. VOLKMER. Yes.

Mr. GORE. It's my understanding that resistance is genetically specific to each individual antibiotic; is that correct?

Dr. CRAWFORD. There is some cross-resistance. There are some instances where one antibiotic, usually one within the same family, transfers resistance, in effect, to other antibiotics.

For instance, there'll be two closely related antibiotics and if a group of bacteria become resistant to one——

Mr. GORE. I see.

Dr. CRAWFORD [continuing]. They will become to the other, even if they haven't been in contact with the other. We have to be careful about that.

Mr. GORE. I see. Well, now, when you say that some of the substitutes do not have a resistance problem, is that because the substi-

tutes are not used in humans, or is it due to some peculiarity in the reaction of the antibiotics to the substitute—I mean, reaction of the bacteria to the substitute?

Dr. CRAWFORD. It's both, Mr. Chairman. Some of them have not been used in human medicine and are no longer used. And in other cases, the former applies. That is, they just don't have the property of producing resistant organisms.

Mr. GORE. All right. Thank you. Thank you for yielding.

Mr. VOLKMER. When do you propose to hold the hearing?

Dr. CRAWFORD. There's a tentative date for late January for the public hearing.

Mr. VOLKMER. Do you know of a study being conducted under the offices of the Animal Health Institute to determine epidemiological facts on the question of transmission—I believe it's on animals to man?

Dr. CRAWFORD. I saw a press release that there was a study being planned, I believe.

Mr. VOLKMER. So that study, of course, probably won't be completed before you make your decision, then?

Dr. CRAWFORD. I'm not sure what their deadline is.

Mr. VOLKMER. OK. Let's see—Dr. Houston, I'd like to get off just a little bit onto something else that concerns some of us that have pork producers, OK?

Dr. HOUSTON. Yes, sir.

Mr. VOLKMER. And particularly on imported meat and we presently have meat imported from various countries.

Dr. HOUSTON. That's correct.

Mr. VOLKMER. Do any of these countries presently use any of these type of tetracycline or penicillin?

Dr. HOUSTON. I'm sure that some of them do, yes. I've——

Mr. VOLKMER. Doesn't Canada?

Dr. HOUSTON. Canada, for example. I'm not sure the extent of use in Denmark and the Netherlands, although I think those uses have been banned there. Again, there's been questions of enforcement that have been raised—arisen earlier here today, but——

Mr. VOLKMER. And in Argentina?

Dr. HOUSTON. We're not bringing in any pork from Argentina.

Mr. VOLKMER. Beef, though.

Dr. HOUSTON. We're bringing in beef and—again, it's not the kind of situation where they'd be using subtherapeutic antibiotics. Most of those are grass-fed cattle, rather than feedlot cattle.

Mr. VOLKMER. All right.

As a general rule, as you—if you have processed, say, processed pork, coming into the United States, do you test it for these antibiotics?

Dr. HOUSTON. We're testing fresh products that are coming in, beef, veal, pork, and some chickens and a few turkeys that come in from Canada. We do monitor the in-country residue testing programs where that product is emanating from. For example, if we're bringing in canned hams from Denmark, we do monitor what they do in that country with respect to residue testing. They must have programs that are equal to ours here.

I might add that I do have the data with me on 1982, 1983 and 1984 results related to samples collected from our monitoring pro-

gram on imports and the results. And for the last three years, we have not had an antibiotic violation in imported meat.

Mr. VOLKMER. Now what do you mean by "antibiotic violation"?

Dr. HOUSTON. Nothing—nothing was over a tolerance.

Mr. VOLKMER. That doesn't mean that it wasn't used.

Dr. HOUSTON. Oh, no, I can't—it may very well be used, but it was in compliance with existing U.S. tolerances and U.S. rules.

Mr. VOLKMER. All right, but what concerns me a little bit, in the event that FDA would, say, go ahead with their order on subtherapeutic use and that Canadian pork producers would continue to use it subtherapeutically——

Dr. HOUSTON. Uh-huh.

Mr. VOLKMER [continuing]. They would still be able to ship that stuff in here, wouldn't they?

Dr. HOUSTON. Yes. We have—we have taken the position that if they—if they control the use and it's not found in the product, we consider it to be in compliance with U.S. standards.

Mr. VOLKMER. What does that do, Dr. Crawford, to your order? Let's say we continue to increase our import of hogs from Canada, which have gone up dramatically, and I start eating ham and bacon and pork chops, things like that?

Dr. CRAWFORD.Well, I would prefer to defer to Dr. Houston on that [laughter] but I bet you won't let me do that, would you?

Mr. VOLKMER. No, I won't let you do that. [Laughter.]

Dr. CRAWFORD. Well, we in FDA, of course, are concerned that—at least our trading partners have about the same spectrum of drugs approved because, you know, we don't believe—we don't believe there's any reason for it to be markedly different, and we don't believe—we don't believe that they ought to draw different conclusions than we do, so we're trying to introduce some international agreements so that we have more or less simultaneous approval of animal drugs worldwide and that we have the same kinds of standards and we're making quite a bit of progress in that area.

If we don't do that kind of thing, then periodically we can come into trade barriers, such as we had with a couple of drugs in the 1970's, and—or about—we may be developing that kind of situation here.

Other international organizations are quite frankly doing more than we are in that regard. The World Health Organization is trying to mediate between nations in this particular area. They have a position on the use of penicillin in animal feed and they have recommended that member nations restrict its use. We don't have any control over Canada and, you know, we can't tell them what to do, but we continue to work with them in this and all other regards. We keep them informed of what we're doing and eventually, I believe there will be the same armamentarium of drugs, you know, in the developed countries approved from country to country. They'll be kind of a common pool.

That is not quite the case yet, but it's getting—it's more—it's better than it was 5 years ago.

Mr. VOLKMER. Dr. Houston, I'd like to ask you about how many—if you can't tell me now, send it to us for the record—what bacteria or what drugs do you test for when you test for, like the imported processed fresh meat?

Dr. HOUSTON. OK, I can supply that for the record, but we do test for a broad range of antibiotics, pesticides, and environmental contaminants.

Mr. VOLKMER. I'd like to have that and——

Mr. GORE. Without objection, we'll hold the record open for it.

[The information follows:]

United States Department of Agriculture
Food Safety and Inspection Service
Washington, D.C. 20250

JAN 18 1985

The Honorable Harold L. Volkmer
U.S. House of Representatives
Committee on Science and Technology
Subcommittee on Investigations and Oversight
822 HOBA #1
Washington, DC 20515

Dear Congressman Volkmer:

On December 18 and 19, 1984, the House Subcommittee on Investigations and Oversight held hearings on the subject of antibiotic resistance in livestock and humans and residual antibiotics in meat and poultry. On December 18th, I testified on behalf of the Department of Agriculture, Food Safety and Inspection Service (FSIS).

At that time, you requested information from FSIS on drugs tested for in imported meat products. In addition, you requested information on our testing data for Canadian hog imports. This information has been provided to the Subcommittee for the record and enclosed is this information for your personal use.

I appreciate your interest of this issue and hope this information is helpful. Should there be anything further I or my staff can assist you with, please let me know.

Sincerely,

Donald L. Houston
Administrator

Enclosures

COMPOUNDS TESTED IN 1983 AND 1984 AND PLANNED TO BE TESTED IN 1985 IN IMPORTED MEAT PRODUCTS UNDER MONITORING AND SURVEILLANCE PROGRAMS (X)

COMPOUNDS	1983	1984	1985
Albendazole			X
1) Antibiotics	X	X	X
Arsenic *		X	
Carbadox		X	
Chloramphenicol		X	X
2) Chloriated Hydrocarbons	X	X	X
Cyromazine (Larvadex)		X	X
Ethylene Dibromide		X	
Hormones	X		
Ivermectin			X
Levamisole			X
2) Organophosphates	X	X	X
4) Sulfonamides	X	X	X
5) Trace Elements	X	X	X
6) UAR		X	X

1) 2) 3) 4) 5) Appendix 1

6) Appendix 2

* Included in 5) with Trace Elements for 1983 and 1985 (Appendix 1)

1) ANTIBIOTICS

Ampicillin
Chlortetracycline
Cloxacillin
Erythromycin
Gentamicin
Lincomycin
Neomycin
Oxytetracycline
Penicillin
Streptomycin
Tetracycline
Tylosin
UMI's

2) CHLORINATED HYDROCARBONS

Aldrin
Benzene hexachloride
Chlordane
Dieldrin
DDT and Metabolites
Endrin
Heptachlor and Metabolites
Lindane
Methoxychlor
Toxaphene
PCB's
Hexachlorobenzene
Mirex
Strobane
Nonachlor
UAR's

3) ORGANOPHOSPHOROUS PESTICIDES

Coumaphos
Dichlorvos (Vapona)
Diazinon
Ethion
Malathion
Parathion
Ronnel
Ruelene
Trichlorfon
Methyl parathion
Dioxathion
Disulfoton
Fenitrothion
Gardona
Chlorpyrifos

4) SULFONAMIDES

Sulfadimethoxine
Sulfamethazine
Sulfathiazole
Sulfaquinoxaline
Sulfabromomethazine

5) TRACE ELEMENTS

Arsenic
Mercury
Copper
Lead
Cadmium
Selenium

Appendix 1

Unidentified Analytical Responses

Unidentified Analytical Response (UAR). An analytical response caused by a compound with chromatographic properties different from those of known references.

Any UAR producing an area response greater than that produced by 0.05 ppm (parts per million) aldrin in the tissue of the CHC (Chlorinated Hydrocarbons) test, or 0.05 ppm ethyl parathion in the tissue of the OP (Organo Phosphates) test, will be reported. Instrument performance characteristics will be as outlined in the Chemistry Laboratory Guidebook and the Chemistry Quality Assurance Handbook. Sample extracts which indicate UARs on the gas chromatograph recording of the screening or official procedure, as described above, will be re-injected and reported.

FSIS will report UARs as they are found in screening or official tests. UAR data will be evaluated for frequency of occurrence, product type, geographic source estimated levels, and any other information suggesting potential for unknown contamination. Further field investigations and analytical work for UAR identification may be performed if indicated after data evaluations. When a UAR is identified, a toxicological evaluation will be made, and if warranted, the compound is recommended for inclusion in the regular monitoring program.

Unidentified Microbial Inhibitor (UMI). Based on microbiological testing, when test results are positive, products are refused entry. Foreign Program's Division Director is advised of the sample violation. UMI are reported as residue violation cases.

Mr. VOLKMER. Right.

The other thing that I would like to ask for you to provide to us the drugs or antibiotics, whatever, that are prohibited for use here in the United States to our processors that are not prohibited in Canada. Hog production.

Dr. HOUSTON. We can supply that for the record.

[The information follows:]

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Food Safety and Inspection Service
Washington, D.C. 20250

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I appreciate your interest of this issue and hope this information is helpful. Should there be anything further I or my staff can assist you with, please let me know.

Sincerely,

Donald L. Houston
Administrator

Enclosures

I. PESTICIDES USED ON LIVESTOCK AND PENS IN CANADA AND NOT APPROVED IN THE U.S.

Total = 1 pesticide compound
Isobornyl thiocyanoacetate

II. DRUGS USED ON LIVESTOCK IN CANADA AND WITH LIMITED APPROVAL IN THE U.S.

DRUG	CANADA	U.S.
1. Chloramphenicol	Approved for use in all food animals with very strict control. Only dispensed by a veterinarian who is obliged by law to take back all left over drugs after treatment of animals in the farm.	Approved only in non-food producing animals.
2. Dimethridazole*	Approved for swine and turkeys.	Approved for turkeys only.

*There is no analytical method. This has been reported to FDA.

Mr. VOLKMER. And then the last question I want you to supply for the record, then, is whether any of those drugs that are prohibited in the United States but not prohibited in Canada cannot be tested for after the meat has been processed.

Dr. HOUSTON. We'll supply that for the record.

Mr. GORE. Without objection, we'll hold the record for those—for those items.

[The information follows:]

The Food Safety and Inspection Service (FSIS) tests imported products for antibiotic residues by using the same procedures as those applied to domestic products. In general, standard laboratory microbiological tests are used first; then, if these tests are positive, appropriate confirmatory procedures are followed. In recent months, questions have been raised about the procedures used to test imported Canadian pork for the presence of chloramphenicol, which is approved for limited use in food animals in Canada but prohibited for such use in the United States.

Canada ships live hogs and fresh, chilled, and frozen pork to the United States. The live hogs are slaughtered in U.S.-inspected establishments, where the carcasses are subject to our domestic residue monitoring program. Canada maintains a similar residue monitoring program over all animals slaughtered in that country. The fresh-frozen pork is subject to further residue testing under our import inspection program when it enters the U.S.

Until September 1984, FSIS used a chemical method to test imported Canadian pork for residues of chloramphenicol. In September, the Agency began using a very sensitive competitive enzyme-labeled immunoassay (CELIA), in addition to the chemical method. Samples that are tested positive for chloramphenicol under CELIA are submitted for further confirmatory testing.

FDA and EPA registration regulations for pharmaceuticals and pesticides require no data or analytical methods for the testing of foods beyond the raw agricultural product stage. Therefore, the FSIS program is based on the control of residues in animals at the time of slaughter. Regarding imported further-processed meat products, the Agency normally tests these products for chlorinated hydrocarbons and trace elements. In the testing of imported processed products for heat-stable compounds, FSIS is further refining and validating analytical methods and reviewing analytical techniques, residue programs, and agricultural practices in foreign countries.

Mr. GORE. And I believe there is one, at least one product that can't be tested for, is that right, Dr. Crawford?

Dr. CRAWFORD. Unfortunately, Mr. Chairman, there are more than one. There are several products that we can't test for. In the United States, these products, by regulation, cannot be approved for use in food-producing animals and that's one of the things we're trying to point out to some of the other countries, particularly Third World countries, that if they are to be trading partners of the United States, that we must be able to detect these products in the meat that comes in.

Mr. GORE. Yeah. There's one problem with Canada on this, too, isn't there, involving pork?

Dr. CRAWFORD. They—they do allow the use of chloramphenicol in some limited circumstances. We do not allow it at all in food-producing animals. That's correct.

Mr. GORE. And we can't detect residues if they bring it in.

Dr. HOUSTON. We can detect residues in—in fresh product, and we have been testing fresh product coming in from Canada. We've also stepped up our testing program for animals that are brought in from Canada and then slaughtered here. We also have data on that which we'll be glad to share with the committee as to our findings, but——

Mr. GORE. OK.

Dr. HOUSTON [continuing]. It's very low.

[The information follows:]

Chloramphenicol in Canadian hogs: data on residues in fresh pork and live hog imports.

Chloramphenicol[1]: Import (POE) Monitoring Samples Collected and Analyzed, January through November 1984

Product	Number of Samples	Number of Violations
Fresh Beef	17	0
Fresh Veal	9	0
Fresh Pork	120	0
Chicken	0	0
Turkey	0	0
Duck/Goose	0	0
TOTAL	146	0

[1]There were 430 samples of live hogs from Canada analyzed during this period. No chloramphenicol residues were found.

Mr. GORE. Mr. Glickman.

Mr. GLICKMAN. Thank you, Mr. Chairman, just a few short questions.

I—Dr. Houston, I previously, when talking to the previous panel of witnesses, made a couple of statements that I think are accurate, but I would just like to get confirmation from you.

One is that the use of antibiotic additives in promoting growth of animals enables farmers to use less feed, on the order of about 5 percent less feed than they would otherwise use. Is that a fair statement?

Dr. HOUSTON. Well, I'm not going to attest to the percentage, but I think it's been well documented that subtherapeutic use leads to increased feed efficiency.

Mr. GLICKMAN. Now, I also made the statement that nearly all poultry, about 70 percent of cattle and 90 percent of hogs raised commercially in the United States ingest subtherapeutic doses of antibiotics at mealtimes. I took that statement out of a—of an article from Chemical Week in October 1984. Is that a fair statement?

Dr. HOUSTON. I—I would dispute that related to poultry. I don't think you will find those levels fed to poultry and I'd ask Dr. Crawford if he could help me on that.

Dr. CRAWFORD. I think you have to make a distinction between whether or not you're talking about penicillin and tetracycline or all antibiotics. Are you talking about all antibiotics?

Mr. GLICKMAN. Well, apparently the article refers to all antibiotics. It doesn't——

Dr. CRAWFORD. Yeah, Dr. Hays mentioned that there are some antibiotics that he referred to as ionophoretic antibiotics that are

used in poultry as coccidiostats. If you add them to the mix, then those figures could well be correct.

Mr. GLICKMAN. I didn't understand that word.

Mr. GORE. Yeah, and could you spell it for the reporter, too.

Dr. CRAWFORD. I'm not here to—[laughter].

Mr. GORE. True enough, you're not. Supply it for the record. [Laughter.]

Dr. CRAWFORD. I can—let me see if I can't do that.

Mr. GORE. But tell me what it means.

Dr. HOUSTON. If Dr. Hays is there, maybe we can ask him.

Dr. CRAWFORD. I'll save him the trouble. I think it's i-o-n-o-p-h-o-r-e-t-i-c. They're also called ionophores. What they are are antibiotic substances. They really don't have any particular antibiotic activity. They are used in ruminants and also in chickens. In cattle, they improve feed efficiency and thereby growth, and in chickens, they're used to control coccidia, which are small protozoan organisms, but they're not used in human medicine, and they're generally thought of as having no applications in human or in veterinary therapy.

Mr. GLICKMAN. OK. Then, if you took that type of drug out, what percentages do you think we'd be talking about, then? The tetracyclines and the penicillins in terms of percentages that are used in poultry, hogs and cattle that are fed in this country?

Dr. CRAWFORD. Well, we'd have to try to supply that for the record. There was a study that was done by the Office of Technology Assessment in 1979 which we could quote. I'm not sure that anything's been done since then.

As I recall, Mr. Glickman, I think those figures were about like that at that time, but we would be pleased to check that for you.

Mr. GLICKMAN. OK.

[The information follows:]

FROM "DRUGS IN LIVESTOCK FEED"—OTA REPORT 1979

More than 40 percent of the antibacterials produced in the United States are used as animal feed additives and for other nonhuman purposes. Nearly 100 percent of poultry, 90 percent of swine and veal calves, and 60 percent of cattle receive antibacterial feed supplementation. About 70 percent of U.S. beef carcass weight comes from cattle that have received weight-promoting feed supplementation.

Mr. GORE. If my colleague will yield, we might ask Dr. Hays from the audience, do you have an estimate, if you take out the—the coccidiostats—that's—whatever, I forget the other—the name——

Dr. CRAWFORD. Ionophores.

Dr. HAYS. Ionophores.

Mr. GORE. Ionophores, so then what—you've got 45 percent according to your figures with them——

Dr. HAYS. My figure of 45 percent, that related to the total amount of antibiotics that were used in animals versus total amount of antibiotics produced in this country. About 45 percent of the total.

Mr. GORE. If you remove that category, then what would happen to that percentage?

Dr. HAYS. I really would—it would be a guess on my part to try to come up with that.

Mr. GORE. Well, whoever has the best way to supply that for the record, we'd like to get it.

Dr. Houston.

Dr. HOUSTON. I was just going to mention, if you're talking about penicillin and the tetracyclines, I think your figure for poultry is quite high.

Mr. GLICKMAN. OK. Would it be a fair statement that a majority of poultry, cattle and hogs raised commercially are fed tetracycline or pencillin as a way to enhance growth and feed efficiency in this country?

Dr. CRAWFORD. You'll have to check that by species. I don't believe you could make the blanket statement that—that the majority of domestic animals are fed these two antibiotics.

Mr. GLICKMAN. OK. I think those statistics are relevant——

Dr. CRAWFORD. OK.

Mr. GLICKMAN [continuing]. For the purpose of what we're talking about.

The other thing concerns the levels therapeutic versus subtherapeutic. In the previous group of witnesses, there was some talk as if we can't really make the determination as to what levels are being fed. Sometimes the implication I got was therapeutic doses may be being fed in—instead of subtherapeutic doses, maybe intentionally, maybe not intentionally.

Do you have any thoughts on that?

Dr. CRAWFORD. Well, I think what would be useful for the record is for us to outline those restrictions that were proposed in 1977. Generally, though, we proposed the ban of all uses of penicillin in animal feed, both therapeutic and subtherapeutic. The term "low level" was intended, I suppose, to apply to the tetracycline uses and—and the reason was that, you know, not all uses of tetracycline were to be restricted and I think they lump those uses that were to be restricted into the low-level category.

I believe with the other panel that that's not particularly descriptive because it is blurred quite a bit. We'll list what we proposed for the record if we may.

[The information follows:]

federal register

TUESDAY, AUGUST 30, 1977

PART IV

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

PENICILLIN

Use in Animal Feed

federal register

FRIDAY, OCTOBER 21, 1977

PART IV

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

TETRACYCLINE IN ANIMAL FEEDS AND TETRACYCLINE CONTAINING PREMIXES

Mr. GLICKMAN. In your proposals, did you ever set forth any standard—standardization of levels that you would recommend, kind of like MDR's [minimum daily requirements], anything that would give the farmers some degree of guidance as to what levels he should not exceed in the feeding of animals?

Dr. CRAWFORD. Yeah. Each approval for each use of every antibiotic that's used in this country is codified by the Food and Drug Administration in the Federal Register, in the Code of Federal Regulations. So we describe explicitly what uses may be legally used in the United States, so those are all there at the present time and also those that we intended to restrict in 1977 were specifically listed.

Mr. GLICKMAN. OK.

Dr. Houston, I—several—a couple of months ago, several Members of Congress wrote Margaret Heckler a letter in connection with the study that was printed in the New England Journal of Medicine, and I don't have—I just—in rereading her letter to me, and I'd like to read a couple of relevant points for the record, and then I would ask that the letter be included in the record, should say—the main operative paragraph:

> We are aware of the comments made by Dr. Houston, Administrator of the Food Safety and Inspection Service, USDA, and certainly agree that the U.S.A. Today article, upon which he commented, contained errors concerning the presence of antibiotics in meat and poultry. The issue at hand regarding the subtherapeutic use of antibiotics is very complex and it is important that the public be accurately informed of the facts.

She goes on to say that the FDA is reviewing the entire question and at the conclusion of the review, the Center for Veterinary Medicine will make a recommendation to the Commissioner of FDA regarding the issue.

But I want to go back to this first sentence there. "We are aware of the comments made by you and certainly agree that the U.S.A. Today article upon which you commented contained errors concerning the presence of antibiotics in meat and poultry." I wonder if you might explain that for us.

Dr. HOUSTON. Well, on September 11, there was an editorial in the newspaper, U.S.A. Today, which said that, "While you may look at the label on your meat product and find out that it may contain salt or a nitrite cure or something else, what you don't really know is that most of the meat and poultry consumed in the United States contains antibiotics," which was very wrong.

What—whoever wrote the editorial mixed up apples and oranges. First of all, they were talking about the resistance phenomenon, which was the main thrust of the article, and then for some reason I can't explain, drew the conclusion that this—this resulted in our meat and poultry supply containing antibiotics, which is not true.

On the 13th of September, I wrote to—a letter to the editor of U.S.A. Today and pointed out that—that they were factually incorrect and I—I went ahead and explained what the true state was with regard to our meat and poultry supply. Subsequently, U.S.A. Today printed that letter, or excerpts from that letter. I did get a followup letter from the editor. I don't have it here, but I'd be glad to supply it for the record. The editor, in fact, said, "Well, maybe we were wrong, but we really had to get the issue out in front of

the public," and I was disappointed in the response. I thought it was—it was almost irresponsible.

Mr. GLICKMAN. OK, well, I was just trying to—I wasn't sure from the tone of Ms. Heckler's letter whether she was kind of giving you a backhanded slap, but apparently from what you're saying is you responded to what you considered to be incorrect arguments presented in their editorial.

Dr. HOUSTON. Yes. I—and I'll be glad to supply my letter to the editor, and I'd also like to supply the editor's letter to me.

Mr. GLICKMAN. I think that would be useful, Mr. Chairman, because it relates specifically to the public information about this subject which——

Mr. GORE. Surely, without objection, we'll include that in the record.

[The information follows:]

United States Department of Agriculture

Food Safety and Inspection Service

Washington, D.C. 20250

JAN 18 1985

The Honorable Daniel Glickman
U.S. House of Representatives
Committee on Science and Technology
Subcommittee on Investigations and Oversight
822 HOBA #1
Washington, DC 20515

Dear Congressman Glickman:

On December 18 and 19, 1984, the House Subcommittee on Investigations and Oversight held hearings on the subject of antibiotic resistance in livestock and humans and residual antibiotics in meat and poultry. On December 18th, I testified on behalf of the Department of Agriculture, Food Safety and Inspection Service (FSIS).

At that time, you expressed interest in an editorial that appeared in USA Today on September 11, 1984. The editorial, "Don't Ignore Risks Livestock Drugs Pose", resulted in my responding to the editor and subsequently, a follow up by the editor to my letter. These three items are enclosed per your request and have also been submitted to the Subcommittee for inclusion in the record.

I appreciate your interest of this issue and hope this information is helpful. Should there be anything further I or my staff can assist you with, please let me know.

Sincerely,

Donald L. Houston
Administrator

Enclosures

Sept. 11, 1984

THE NATION'S NEWSPAPER
USA TODAY
PUBLISHED BY GANNETT

OPINION

The Debate: DRUGS IN MEAT

Today's debate includes our opinion that routinely giving antibiotics to livestock is a health threat that must be taken seriously, an opposing view from Virginia, other views from California, Massachusetts, and Nebraska, and voices from across the USA.

Don't ignore risks livestock drugs pose

If you read the labels on the food you buy in the supermarket, you think you know what you are eating.

Pick up a pound of bacon. The label tells you that it contains preservatives. Select a package of chicken — it lists the calories, carbohydrates, and protein. Get some ground round — it is marked Grade A choice.

But those packages contain a surprise no label reveals. Most of the pork, poultry, and beef you buy contains antibiotics. It isn't put there to keep you well. It is there because farmers feed their livestock a daily dose of these miracle drugs to help them grow fatter faster.

Those same antibiotics can end up in your grocery cart, on your plate, and in you.

Last week, researchers at the Centers for Disease Control in Atlanta reported on 18 Midwesterners infected with germs resistant to antibiotics. The researchers said the germs came from South Dakota beef cattle.

To fatten them, the cattle were fed steady doses of antibiotics. They developed a resistance to the drugs. That resistance was transferred to the humans.

Twelve of these people later took penicillin for sore throats, earaches, and bronchitis. But because they had acquired the resistant germs, the drug worked no miracles. Eleven people were hospitalized. One died.

This doesn't mean that everybody who eats meat or poultry and takes antibiotics will stay sick. But this research seems to establish that feeding livestock drugs can render antibiotics ineffective for treating disease.

Feeding antibiotics to farm animals is a big business. Thirty years ago, farmers bought less than 1 million pounds of the drugs. Today they buy 15 million pounds and spend more than $100 million a year on them.

But what is efficient for farmers and profitable for drug makers could be a threat to public health.

The real risk is that excessive use of antibiotics in animal feed could render these miracle drugs impotent when people really need them — to fight off infection.

Some argue that the new study is flawed and inconclusive. They ignore the efforts of many American scientists who have tried for years to get animals off antibiotics.

In 1978, the Food and Drug Administration urged limiting livestock drug use, but Congress wanted more studies.

This new study should set off an alarm bell for the FDA: It must re-examine the threat to human health.

The link to human health should push farmers to find alternatives to antibiotics. Some European nations already limit their use. And grazing animals may be safer than fattening them with drugs in meat factories.

Antibiotics have been a godsend to humans. They can cure a child's ear infection and save a life threatened by pneumonia. But if they are overused — and abused — our miracle drugs won't work miracles any more.

QUOTELINES

"If you took these drugs away from the farmer, you would be costing the consumer over $3 billion in increased meat prices in the first year."
— *Booker T. Alford, American Cyanamid*

"Adding antibiotics to animal feed should be re-examined and the risks and benefits weighed more carefully."
— *Scott Holmberg, Centers for Disease Control*

"City people use cleansers, sanitizers, bug bombs, weed killers, solvents. Half the kids are on dope, and their parents are on tranquilizers. These things are just as dangerous as the drugs we give our animals."
— *Art Lehmann, Illinois hog farmer*

"Apparently the drug companies and the government want to see dead bodies before they admit that there is an inherent danger here."
— *Dwight Hirsh, University of California at Davis*

(continued)

(1 of 5)

United States Department of Agriculture
Food Safety and Inspection Service
Washington, D.C. 20250

Letter to the Editor
USA Today
P.O. Box 500
Washington, DC 20044

13 SEP 1984

Dear Editor:

Your September 11 editorial discussing a recent study by the Centers for Disease Control ("Don't Ignore Risks Livestock Drugs Pose"), may unduly alarm consumers. I want to clarify some points about the findings of the study and also assure consumers that they can be fully confident of the safety of the meat and poultry supply.

First, it must be pointed out that the CDC study did not say that meat and poultry sold in the consumer marketplace contains antibiotics as your editorial states. Your statement was factually incorrect. As part of the Federal meat and poultry inspection program, USDA routinely analyzes meat and poultry samples for drug or chemical residues. The incidence of positive findings of antibiotics is very low and contradicts your statement that "most of the pork, poultry and beef you buy contains antibiotics."

Second, it should be pointed out that Salmonella food poisoning, the cause of illness in the patients studied by CDC, is largely preventable if consumers follow basic food safety rules. USDA has long recognized the need for educating consumers about proper storage and cooking of meat and poultry to prevent food poisoning, especially Salmonella which scientists generally agree cannot be completely eliminated from the food supply. The importance of handling meat properly was underscored by the CDC study. The authors noted that 7 of 10 Minnesota patients with antibiotic-resistant salmonella poisoning were housewives who handled--and even tasted--raw hamburger. In contrast, other family members who ate the cooked meat did not become ill.

Consumers who follow these food safety rules should be protected from Salmonella food poisoning:

- Cook red meat to 170°F (gray center). Poultry should reach 185°F and show no red at the joints. Don't eat raw meat.
- Wash hands, dishes, utensils, and cutting boards or counters thoroughly after they've been used with raw meat or poultry and before they are used with cooked food. This prevents the spread of bacteria from the raw to cooked food.
- Keep food hot until served and eaten, and refrigerate or freeze between use. Do not leave food at room temperature for more than 2 hours.

Letter to the Editor

* Wash hands in hot, soapy water before preparing food. Keep pets and insects away from food and kitchens. Animals and insects carry a variety of viruses and bacteria including salmonella.

Any consumer who has a specific question about meat or poultry can call the USDA Meat and Poultry Hotline at 202-472-4485.

Sincerely,

Donald L. Houston
Administrator

Rec'd. ExS:
Referred:
TO:
DUE:

September 21, 1984

Donald L. Houston
Administrator
Food Safety and Inspection Service
United States Department of Agriculture
Washington, D. C. 20250

Dear Mr. Houston:

Thanks you for your letter of September 13. We ran excerpts of it on September 24 in our Letterline column.

After reviewing our editorial, your letter and other articles, I think you are right that we oversimplified the process through which organisms resistant to antibiotics migrate to humans. But since your tests do show that a "low incidence" of antibiotics are present in meat, we believe it is still a practice that the public ought to be genuinely concerned about, and we do not believe that we overstated the dangers or unduly alarmed the public.

The CDC study shows that the wholesale feeding of antibiotics to livestock may constitute some danger to human health, and that was the main thrust of our editorial. We believe that's accurate, and important for the public to know. In addition, we offered our readers other views from experts.

Thanks again for your thoughtful criticism.

Sincerely,

Peter Prichard
Associate Editorial
Director

PP/bs

Mr. GLICKMAN. I thank you, Mr. Chairman. I have no further questions.

Mr. GORE. I'd like to thank both of you. Let me just conclude by saying, Dr. Crawford, I get the impression that FDA is moving toward the action that was suspended in 1977. Is that an accurate conclusion?

Dr. CRAWFORD. Well, we were moving toward an analysis until the development of this imminent hazard petition——

Mr. GORE. Yeah.

Dr. CRAWFORD [continuing]. So we are having to consider it and all its aspects before we proceed with the other decision.

Mr. GORE. Yeah.

Mr. VOLKMER. Mr. Chairman.

Mr. GORE. Yes.

Mr. VOLKMER. I'd like to ask Dr. Crawford a question with regard to a statement that was made by the previous panel——

Mr. GORE. Go ahead.

Mr. VOLKMER [continuing]. By one of the members, and that is that you said that in the estimate of the number of cases that we have of Salmonella that—in the United States—that only about 1 percent are actually reported and go through the process to get to the Centers for Disease Control as a total number.

Would you agree or disagree with that?

Dr. CRAWFORD. I don't have any knowledge of—direct knowledge of how they arrive at those projections. I've seen that quoted here and in other countries, too, as being an indication, you know, of about how many are not reported, but that's not my field of expertise.

Mr. VOLKMER. Have you examined the study that was made, the King County study in Seattle?

Dr. CRAWFORD. We are subjecting it to a peer review now and we have not finished our analysis of it.

Mr. VOLKMER. Would that study, with the number of instances there relating to—I don't know how you pronounce the other disease that was reported there——

Dr. CRAWFORD. Campylobacter.

Mr. VOLKMER. Yeah, having more instances there than actually the Salmonella, and not the instances of number of population——

Dr. CRAWFORD. Well, we——

Mr. VOLKMER [continuing]. Actually done on every instance, was it not?

Dr. CRAWFORD. Yeah, we're not sure what that means. On the face of it, it would tend to make you wonder if there weren't more cases of Campylobacter than Salmonella—and I assume that's what you're getting at——

Mr. VOLKMER. Plus there aren't that total number in the United States, either, if there's only that number in Seattle.

Dr. CRAWFORD. Yes, so we—you know, we'll have a statement when we finish the peer review of that contract, but we're not sure what that means at this point.

Mr. VOLKMER. I mean, if you take the whole population that was done over that 18-month period——

Dr. CRAWFORD. Right.

Mr. VOLKMER. If you take the number of instances——

Dr. CRAWFORD. Uh-huh.

Mr. VOLKMER [continuing]. It doesn't appear that that would be correct.

Thank you, Mr. Chairman.

Mr. GORE. Thank you very much, and I'd like to thank both of you for being here today and helping us. Thank you.

Our last—our third and last panel of witnesses is a large one. I'd like to call them to the witness table at this time and ask the staff to put a couple more chairs up there.

Dr. Karim Ahmed, senior staff scientist and research director with the Natural Resources Defense Council; Dr.—excuse me, Sarah Chasis, counsel for the NRDC; Dr. Wes Bonner, with the National Cattlemen's Association in Englewood, CO; Lee Boyd, vice president for feed control and nutrition with the American Feed Manufacturers Association; Dr. Richard Gustafson, associate research fellow with American Cyanamid; and Mike Wehler, chairman of the antibiotic task force with the National Pork Producers Council.

If you can all squeeze in here, we'll try to get started here momentarily.

Thank you all for coming. I would like to remind you that, without objection, your full prepared statements are going to be included in the record in full. We have had a rather full discussion today about many of these issues, and with that in mind, if, in looking at your statements, you feel you can summarize portions of them, that would be appreciated. We're going to take all of the witnesses before asking questions, so let's go ahead and get started.

Dr. Karim Ahmed, senior staff scientist and research director with the Natural Resources Defense Council, our first witness. We're glad to have you here and please proceed.

STATEMENT OF DR. A. KARIM AHMED, SENIOR STAFF SCIENTIST AND RESEARCH DIRECTOR, NATURAL RESOURCES DEFENSE COUNCIL, ACCOMPANIED BY SARAH CHASIS, COUNSEL, NATURAL RESOURCES DEFENSE COUNCIL; DR. WESLEY BONNER, NATIONAL CATTLEMEN'S ASSOCIATION; CHARLES W. KLINGER, DIRECTOR OF REGULATORY COMPLIANCE, CENTRAL SOYA CO., INC., FORT WAYNE, IN, ACCOMPANIED BY LEE H. BOYD, VICE PRESIDENT, FEED CONTROL AND NUTRITION, AMERICAN FEED MANUFACTURERS ASSOCIATION; DR. RICHARD H. GUSTAFSON, ASSOCIATE RESEARCH FELLOW, AMERICAN CYANAMID CO.; AND MIKE WEHLER, CHAIRMAN OF THE ANTIBIOTIC TASK FORCE, NATIONAL PORK PRODUCERS COUNCIL

[The biographical sketches of Dr. Ahmed and Ms. Chasis follow:]

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**Biographical Sketch of
Natural Resources Defense Council
Witnesses**

Dr. A. Karim Ahmed is a Senior Staff Scientist and Research Director at the Natural Resources Defense Council. Sarah Chasis is a Senior Staff Attorney with the Council.

Dr. Ahmed received a Ph.D. in biochemistry from the University of Minnesota in 1969. He has been on the staff of NRDC since 1974 and since 1975 has been an Adjunct Associate Professor at the State University of New York, College at Purchase where he teaches environmental toxicology. Ms. Chasis graduated from Smith College in 1969 and received her law degree from New York University School of Law in 1972.

Both Dr. Ahmed and Ms. Chasis have worked on the issue of antibiotics in animal feed for the last several years. When industry petitioned FDA in 1981 to vacate proposed actions that would limit the use of antibiotics in animal feed, they countered with an NRDC petition in opposition. In 1983, they filed extensive comments vigorously opposing FDA's proposed rule that would have allowed new approvals of

subtherapeutic use of penicillin and tetracycline in animal feeds for the first time in ten years.

On October 22, 1983 they prepared and sent a letter from NRDC to President Reagan and Margaret Heckler requesting a ban on the subtherapeutic use of penicillin and tetracyclines in livestock feeds. Over 300 scientists supported the requested ban, including some of this country's leading scientists, physicians, and biologists.

Most recently, Dr. Ahmed and Ms. Chasis prepared and filed an NRDC petition with the Secretary of Health and Human Services asking her to act immediately to suspend approval of subtherapeutic uses of anitbiotics in animal feeds.

NRDC is a non-profit national environmental organization with over 42,000 members and contributors in the United States. Its staff of lawyers and scientists work on a wide-range of environmental issues including air and water quality toxic substances and hazardous waste, land use and coastal zone management, energy policy and the global environment.

Dr. AHMED. Thank you, Mr. Chairman.

We appreciate this opportunity to appear before this committee to testify on issues related to the development of resistance to antimicrobial drugs. My name is Karim Ahmed. I am the senior staff scientist and research director at the Natural Resources Defense Council, and accompanying me is Ms. Sarah Chasis, who is our senior staff attorney.

This testimony is being presented on behalf of the Natural Resources Defense Council, Congress Watch, Public Voice, Industrial Union Department of the AFL-CIO, United Steelworkers of America, Center for Science in the Public Interest, and the National Network to Prevent Birth Defects.

Our testimony will focus specifically on the issue of subtherapeutic uses of penicillin and tetracyclines in animal feed.

Because of recent studies closely linking such use of these drugs with human disease, NRDC last month petitioned the Secretary of Health and Human Services for an immediate suspension of approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds. A copy of the NRDC's letter to the Secretary and accompanying petition are attached to this testimony.

Before I go any further on the issue of the risks that are associated with the use, I'd like to very briefly mention, Mr. Chairman, what our efforts have been in this area in the past.

In October 1983, we submitted a letter to the White House and to the Secretary of Health and Human Services on behalf of 300 lead-

ing scientists in this country asking that this particular action that has been pending before the FDA be taken with respect to penicillin and tetracyclines. These included leading scientists in the leading medical colleges and universities in this country, including Government institutes and research organizations.

Our present petition has been prepared with our scientific advisory panel which includes as our chairman, Dr. Jere Goyan, who is presently the dean of pharmacy at the University of California in San Francisco and formerly Commissioner of FDA. It includes Dr. Stuart Levy, who will be a witness at your hearings tomorrow, who is at Tufts Medical School; Dr. Richard Novick, who is with the Public Health Research Institute in New York City, a leading plasmid biologist; Dr. Stanley Falkow, professor of biology at Stanford University; and Dr. Dwight Hirsch, professor of veterinary medicine, University of California, Davis.

So, in essence, what we have to present to you is not only the concerns of the groups that I just mentioned, Mr. Chairman, but the concerns of the scientific community at large and the people who have worked with us very closely for the last 3, 4 years to develop our position on this issue.

Let me next, in the interest of time, just summarize for you, Mr. Chairman, what our concerns are in terms of the risk. We have estimated the risk in terms of mortality and morbidity by using three different approaches. In our testimony here, we start off on the first to determine the mortality rate that might be linked to the use of these two drugs subtherapeutically in terms of the information we were able to gather from the Centers for Disease Control, using the information that's been developed recently by the center and making certain assumptions as to the relative use of these two drugs in the marketplace in the livestock industry.

Our first method of determining mortality rate on an annual basis was to consider the fact that 40,000 cases of Salmonella infection are reported each year in the United States. These are reported cases, and we use the conservative assumption that 20 percent of Salmonella strains are resistant to one or more antibiotics. And then, using a piece of information that was recently gathered by Centers for Disease Control, that for resistant Salmonella infection, there is a 4.2-percent mortality rate and the fact that 69 percent of all Salmonella outbreaks can be traced to animal sources and the fact that penicillin and tetracycline constitute 50 percent of all antibiotics produced in this country; I have, on page 4, footnote 4, the actual numbers that we were able to gather from the U.S. Trade Commission. This is the one question that you asked, Mr. Chairman, earlier.

In 1982, there were 9.5 million pounds of pencillin used in this country. Tetracycline amounted to 7.2 million pounds, and, which together with penicillin, accounted for 51.5 percent of all antibiotics produced in this country.

After making the assumption that 50 percent of antibiotics are used in animal—livestock—industry, we come to the conclusion that approximately 116 deaths a year could be associated annually with Salmonella from resistant strains from the use of these 2 drugs.

Another method we used to derive the mortality rate was to start out by looking at the approximate number of deaths that could be associated with Salmonella outbreaks in this country, and from Centers for Disease Control, the figures come out to around 1,000 to 1,500.

Using these numbers and using some other figures we got from the CDC—for example, the Holmberg study indicated 76.5 percent of all fatal Salmonella infections associated with resistant bacteria, and using the same ratios I mentioned earlier, we come up with a somewhat higher figure of around 264 deaths per year associated with the use of these 2 drugs. So we estimate that anywhere between 100 and 300 deaths per year could be associated with the use of these drugs.

On the question of morbidity, the issue really involves reported versus unreported cases. We use the CDC figure, again the fact that only 1 percent of all Salmonella cases are reported and using the same ratios that I mentioned earlier, Mr. Chairman, we come to a figure of over 270,000 cases of nonfatal Salmonella could be attributed to the use of these 2 drugs in animal feed.

So, based upon this information, we felt justified to bring before the—to the attention of the Secretary of Health and Human Services the need to ban these two products immediately from the marketplace and I'll have Sarah Chasis give the legal arguments behind our petition at this point.

Ms. CHASIS. Thank you, Mr. Chairman. I'm a senior staff attorney with NRDC.

In 1977, based upon the existing data, FDA proposed to withdraw approval of all subtherapeutic and therapeutic uses of penicillin in animal feeds and most subtherapeutic uses of tetracycline in animal feeds.

After it became apparent that FDA was serious about protecting the public health by withdrawing the approvals, industry appealed to another forum, Congress. Committee reports on several appropriation bills earmarked funds to be used for studies to determine the extent of the health threat from subtherapeutic uses of antibiotics in animal feed. Reports also directed FDA to hold further regulatory action in abeyance until the completion of these studies. Most recently, the 1984 Senate report on the appropriations bill directed FDA to review the results of the research now completed, report on its conclusions and probably future actions in hearings on FDA's 1986 appropriations, and withhold further regulatory action until such report to the Appropriations Committee had been made and considered by the committee.

To date, FDA has followed these congressional directives. It has withheld regulatory action and instead has undertaken additional studies. Now it has completed those studies.

These studies, taken together, significantly strengthen and lend support to FDA's initial proposal to withdraw approvals for these drugs. We believe, Mr. Chairman, that the time is long overdue for FDA to act and for Congress to remove the constraints they have imposed on the agency. FDA should proceed to withdraw the approvals of these drugs as it initially proposed to do in 1977.

Because completion of withdrawal proceedings could take as long as 3 years, the Secretary of HHS should act immediately to sus-

pend approvals pending completion of expedited withdrawal proceedings.

Section 512(e)(1) of the Food, Drug and Cosmetic Act authorizes the Secretary of HHS to take such action if there is an imminent hazard to public health. NRDC has petitioned the Secretary under this section based on its risk assessment, showing that at least between 100 and 300 human deaths annually are attributable to subtherapeutic use of penicillin and tetracycline in animal feeds.

Our petition is also based on evidence that there would be no risk to human health from suspending these approvals and no significant risk to animal health. Also, there is no effective alternative means to protecting public health other than suspension.

For these reasons, we believe the Secretary should immediately suspend approvals.

We urge the members of this committee and others in Congress to support and encourage immediate action by the Secretary of HHS and FDA to protect the public health from this serious threat. These agencies should be allowed to address this problem unhampered by congressional constraints. Indeed, we believe Congress should encourage the Secretary to act expeditiously on our petition and the FDA to proceed immediately with final withdrawal proceedings.

Thank you, Mr. Chairman.

[The prepared statements of Dr. Ahmed and Ms. Chasis follow:]

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TESTIMONY

OF THE

NATURAL RESOURCES DEFENSE COUNCIL,

CONGRESS WATCH,

PUBLIC VOICE,

INDUSTRIAL UNION DEPARTMENT
AFL-CIO,

UNITED STEELWORKERS OF
AMERICA,

CENTER FOR SCIENCE IN THE
PUBLIC INTEREST,

AND NATIONAL NETWORK TO
PREVENT BIRTH DEFECTS

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS & OVERSIGHT
OF THE
HOUSE OF REPRESENTATIVES SCIENCE & TECHNOLOGY COMMITTEE

December 18, 1984

Dr. A. Karim Ahmed, Ph.D.
Senior Staff Scientist
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We appreciate this opportunity to appear before the Subcommittee on Oversight and Investigations of the House Science and Technology Committee to testify on issues related to the development of resistance to antimicrobial drugs. This testimony is presented on behalf of the Natural Resources Defense Council (NRDC), Congress Watch, Public Voice, Industrial Union Department AFL-CIO, United Steelworkers of America, Center for Science in the Public Interest and National Network to Prevent Birth Defects. Our testimony will focus specifically on the issue of the subtherapeutic use of penicillin and tetracyclines in animal feed.

Because of recent studies closely linking such use of these drugs with human disease, NRDC last month petitioned the Secretary of Health and Human Services (HHS) for an immediate suspension of approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds. A copy of NRDC's letter to the Secretary and accompanying petition are attached to this testimony.

Long-term, low dose (subtherapeutic) use of penicillin and tetracyclines in animal feed poses a serious threat to public health. NRDC estimates that each year's delay in implementing a ban on such use of these drugs will result in between 100 to 300 deaths annually.

NRDC's assessment of the risk from use of these drugs, upon which its petition to the Secretary is based, is explained below. The other grounds for petitioning the Secretary under the

imminent hazard provision of the Food, Drug & Cosmetic Act are also discussed. Finally, our testimony concludes with a recommendation regarding what Congress should do to deal with this important issue.

I. ASSESSMENT OF RISK

As part of its petition to the Secretary of HHS, NRDC prepared a preliminary risk analysis which projects a mortality and morbiity rate linked to the use of penicillin and tetracyclines in animal feed. Our analysis shows that between 100 and 300 deaths and over 270,000 non-fatal cases of Salmonella poisonings each year may be attributed to such use of these drugs.

A. Estimated Annual Mortality Linked to Animals Fed Subtherapeutic Doses of Penicillin and Tetracyclines in Animal Feed

1. Method 1

According to the Centers for Disease Control, approximately 40,000 cases of Salmonella infection in humans are reported each year in the United States.[1] Since 20-30% of Salmonella strains isolated from humans are resistant to one or more antibiotics,[2] a

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1 Personal communication with Scott D. Holmberg, M.D., Enteric Disease Branch, Centers for Disease Control, Atlanta, Georgia. This estimate is supported by the figure of 35,625 cases reported in 1981, up to 10,000 from ten years earlier, reported by Riley, Importance of Host Factors in Human Salmonellosis Caused by Multiresistant Strains of Salmonella, 149 J. of Infectious Diseases at 378 (1980).

2 Holmberg, Wells & Cohen Animal-to-Man Transmission of Antimicrobial-Resistant Salmonella: Investigations of U.S. Outbreaks, 1971 - 1983, 225 Science 833 (1984)

conservative estimate of the number of cases due to resistant strains of Salmonella bacteria is 8,000 (20%). Of these, an estimated 336 cases may be fatal, assuming a 4.2% fatality rate for resistant Salmonella infections.[3] Since 69% of reported Salmonella outbreaks involving antibiotic-resistant strains are traceable to animal sources, of the estimated 336 deaths from resistant bacteria 69%, or 232, are attributable to resistant bacteria from animal sources. Penicillin and tetracyclines constitute approximately 50% of all antibiotics produced in the United States.[4] We can assume that a similar proportion of penicillin and tetracyclines is used in the livestock industry (although the percentage may in fact be higher) since approximately half the antibiotics produced in the United States is used in the animal livestock industry.[5] Next, since subtherapeutic antibiotic use constitutes most of all antibiotic use for animals, we assume that this use is responsible for virtually all antibiotic resistance among animal bacterial

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3 Id.

4 Personal communication with Edward Capeuchelli, Energy and Chemical Division, U.S. Trade Commission, Washington, D.C. In 1982, penicillin (9,507,000 lbs) and tetracycline (7,243,000 lbs) accounted for a total of 51.5% of the 32,518,000 lbs. of antibiotics produced in the U.S.

5 National Academy of Sciences, The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds 7-8 (1980).

populations.[6] Thus, if half the resistant strains of Salmonella from animal sources have emerged under the selective pressure of subtherapeutic use of penicillin and tetracyclines, it is estimated that 116 (0.5 x 232) Salmonella deaths each year are associated with subtherapeutic use of these antibiotics.

2. Method 2

An alternative method of risk estimate is based on the actual mortality incidence from Salmonella infections. According to statistics compiled by the Centers for Disease Control, between 1,000 and 1,500 deaths each year are associated with Salmonella outbreaks in the United States.[7] The recent Holmberg, et al., study indicates that 76.5% of all fatal Salmonella infections are associated with resistant bacteria.[8] Application of this percentage to the lower estimate of 1,000 Salmonella fatalities per year gives an estimate of 756 deaths per year from resistant strains of Salmonella. As in the first method of analysis, the number of fatal resistant infections traceable to animal sources is estimated based on the finding that 69% of

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6 The remaining use of antibiotics in animals is for therapeutic treatment which is episodic in nature and of limited duration. It is reasonable to assume that such use does not contribute significantly, if at all, to the longterm, sustained development of antibiotic-resistant bacterial strains in animals.

7 Private communication with Scott D. Holmberg, M.D., Enteric Diseases Branch, Centers for Disease Control, Atlanta, GA.

8 Holmberg, supra p.3, 225 Science 833-834. Holmberg found 13 deaths from 312 Salmonella cases associated with resistant bacteria and 4 deaths from 1,912 Salmonella cases associated with sensitive strains. Thus, out of a total of 2,224 cases, 13 out of 17 deaths, or 76.5% were associated with resistant Salmonella strains.

multiply resistant Salmonella outbreaks are traceable to animal sources, giving a figure of 528 deaths per year. As in the previous analysis, it is assumed that penicillin and tetracyclines constitute 50% of the antibiotics used subtherapeutically in animal feed and that virtually all antibiotic-resistant strains of Salmonella of animal origin are linked to subtherapeutic use of antibiotics in animal feed. Thus, an estimated one-half of the 528 fatalities from infections by resistant strains result from subtherapeutic use of penicillin and tetracyclines, or 264 deaths per year.

B. Estimated Annual Morbidity Linked to Animals Fed Subtherapeutic Doses of Penicillin and Tetracyclines in Animal Feed

Resistant strains of bacteria emerging in animal populations given subtherapeutic amounts of penicillin and tetracyclines in animal feed could be responsible for an estimated 270,000 non-fatal cases of Salmonella each year. In these 270,000 cases the resistance of the bacteria to antibiotic treatment may increase the duration of the illness and its symptoms.

This estimate is arrived at by means of the following analysis. Approximately 40,000 cases of Salmonella bacterial infection are reported each year.[9] An estimated 20% of these cases, or 8,000 cases, are infections by resistant strains of bacteria.[10] Of these estimated 8,000 reported cases of infection by resistant Salmonella, 69%, or 5,520, can be attributed to

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9 Supra, p.3.

10 Id.

animal sources, and 50% or 2,760, of these are attributed to bacterial strains whose resistance is a result of subtherapeutic use of penicillin and tetracycline in animal feeds.[11] Since only approximately 1% of all cases of Salmonella infection are clinically reported,[12] the 2,760 figure is multiplied by one hundred, giving an estimate of over 270,000 cases of non-fatal salmonellosis each year due to strains whose resistance is associated with the subtherapeutic use of penicillin and tetracyclines in animals feeds.

II. OTHER GROUNDS FOR NRDC'S IMMINENT HAZARD PETITION

NRDC demonstrated in its petition to the Secretary that the criteria for a finding of "imminent hazard" had been met and, consequently, the Secretary should act immediately to suspend approval of subtherapeutic use of penicillin and tetracylcines in animal feed.

Section 512(e)(1) of the Food, Drug and Cosmetic Act, 21 U.S.C. § 360b(e)(1), authorizes the Secretary of Health and Human Services to suspend approval of an application for use of a new animal drug if there is an "imminent hazard" to the health of man or of the animals for which the drug is intended. The criteria the Secretary has proposed be used in determining whether an "imminent hazard" exists and, consequently, whether approval of a drug application should be suspended, pending withdrawal

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11 Supra, p.4
12 Private communication with Scott D. Holmberg, M.D., Enteric Branch, Centers for Disease Control, Atlanta, GA.

proceedings, are:

(A) The likelihood that, after the customary administrative process is completed, the product will be withdrawn from the market;

(B) The severity of the harm that could be caused by the product during the completion of customary administrative proceedings to withdraw the product from the market;

(C) The likelihood that the product will cause such harm while the administrative process is being completed;

(D) The risk to the health of humans or animals currently taking the product that might be occasioned by the immediate removal of the product from the market, taking into account the availability of alternatives to the product and the steps necessary for affected persons to adjust to these other alternatives; and

(E) The availability of other approaches to protect the public health.

44 Fed. Reg. 48,979 (to be codified at 21 C.F.R. §2.1) (proposed August 21, 1979) (proposed rule establishing imminent hazard criteria and procedure).

Similar criteria were employed by then-Secretary Joseph Califano in suspending approval of new human drug applications for phenormin hydrochloride. Order of the Secretary Suspending Approval, New Drug Application for Phenformin (July 25, 1977). These criteria were upheld in the face of legal challenge. Forsham v. Califano, 442 F. Supp. 203 (D.D.C. 1977), dismissed as moot per curiam, No. 77-1478 (D.C. Cir. 1979).

A. Likelihood of Withdrawal

The first criterion to be used in deciding whether an imminent hazard exists is the likelihood that FDA approval of the drug application will be withdrawn. 44 Fed. Reg. at 48,982.

Section 360b(e)(1)(B) requires the FDA to withdraw approval of a new animal drug application when new evidence shows that the drug is not shown to be safe. Because new evidence clearly demonstrates that subtherapeutic use of penicillin and tetracyclines in animal feeds is not shown to be safe, there is a substantial likelihood that the FDA will withdraw its approval.

B. Severity and Likelihood of Harm

The second and third criteria to be used in determining whether use of a drug constitutes an imminent hazard are the severity and likelihood of harm that could occur pending the completion of customary administrative proceedings to withdraw the product from the market.

NRDC's preliminary risk assessment demonstrates that hundreds of human deaths will occur each year and several hundred human deaths prior to the completion of withdrawal proceedings,[13] if subtherapeutic use of penicillin and tetracyclines in animal feed is allowed to continue.

C. Risk to Human or Animal Health of Suspending Subtherapeutic Uses of Penicillin & Tetracyclines in Animal Feed

The fourth criterion used in deciding whether an imminent hazard exists is the risk to the health of humans or animals that would result from the immediate removal of the drug. No signifi-

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13 It has been estimated that completion of withdrawal proceedings could take 3 years. Letter from Alair Townsend, Assistant Secretary for Management & Budget, HHS, to Hon. Jamie I. Whitten Chairman, House Committee on Appropriations (June 23, 1981).

cant risk would be associated with suspending approval of subtherapeutic uses of penicillin and tetracyclines in animal feed. No potential health risks to humans have been discussed in the literature. The health risk to animals can be greatly minimized, or even eliminated, by use of substitute antibiotics and better farming practices.

1. Risks To Human Health

NRDC has found no evidence or even suggestions in the medical and public health literature that withdrawal of penicillin and tetracyclines from subtherapeutic uses in animal feeds would result in risks to human health. The only effect on humans would be economic. A number of studies have modelled production and prices of meat if various combinations of antibiotics are banned from animal feed. Results indicate that economic losses to consumers will be felt mostly in the first few years of a ban[14] and that, over the longer term, use of existing alternatives to these antibiotics would substantially mitigate the economic effects on consumers.[15]

2. Risks to Animal Health

It has been claimed that subtherapeutic doses of antibiotics are fed to farm animals in order to (1) prevent disease outbreaks

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14 U.S. Dept of Agriculture, Economic Effects of a Prohibition on the Use of Selected Animals Drugs 2 (1978).

15 Headley, J.C., Economic Aspects of Drug & Chemical Additives, pp.30-31, paper commissioned for OTA study, Drugs in Livestock Feed (1979).

among livestock, (2) increase feed efficiency (weight gain per unit of food) and (3) promote growth.

Withdrawing subtherapeutic uses of penicillin and tetracyclines would serve to eliminate these intended benefits. Decreased feed efficiency and slower growth are purely economic effects. They pose no health risks to the animals. The sole health risk to animals, then, is the hypothetical increased likelihood of disease. This risk is not severe, since diseased animals, whether or not they are already receiving low levels of antibiotics, are typically treated with therapeutic doses of antibiotics. NRDC is not advocating ban on treatment of actual disease with antibiotics. Additionally, it is increasingly recognized by the livestock industry that antibiotics at any dose level do not treat infection caused by resistant organisms.

Two effective alternatives exist to minimize the incidence of illness among farm animals. The first and simplest alternative is for farmers to substitute other antibiotics for penicillin and tetracyclines in animals feeds. Alternative antibiotics currently used in animal feeds include bacitracin, nitrofurazone, banbermycin, novobiocin, monensin, tylosin and others.[16] Tylosin and bacitracin are considered excellent substitutes for tetracyclines and penicillin in swine, chicken

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16 Report of the Comptroller General of the United States, U.S. General Accounting Office: Need To Establish Safety And Effectiveness of Antibiotics Used In Animal Feeds 4 (1977). Hagsten, I. et al., Effect of Banbermycin and Tylosin on Performance of Growing-Finishing Swine, 50 J. Animal Sciences 484 (1980).

and turkeys.[17] In the case of pork and beef, tylosin and bacitracin are considered viable substitutes.[18]

Another method of reducing the incidence of disease in farm animals involves altering farming practices. Intensive farming practice confines animals, usually with very little room for each animal, for the most or all of their lives, and rigidly controls their diet, thereby altering their physical and behavioral characteristics. The confinement and crowding creates a great deal of stress for animals, and this stress increases the risk of disease. Since the animals are so crowded, disease spreads quickly.

Non-intensively farmed animals are not confined as much, may have access to the outdoors and are weaned later. Each of these practices lessens the stress on the animals. This type of farming is relatively low cost, since the farmer need not buy the expensive facilities and equipment needed by the confinement farmer.[19] For farms with less intensive animal-raising practices and good managment, subtherapeutic levels of antibiotics may not be necessary.

Thus, there is not a significant health risk to animals associated with banning subtherapeutic doses of penicillin and tetracyclines from animal feed. On the contrary, there is a

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17 Headley, supra p.10, at 30.

18 Id.

19 Statement of Charles Henry Hassebrook, Center for Rural Affairs, Walthill, Nebraska, before the House Committee on Interstate and Foreign Commerce, Subcomittee on Health and the Environment, Serial No. 96-169, June 12 and 24, 1980.

positive benefit, since if the animals should become ill, there is at least the chance of treating them if the causative agent is a sensitive bacterial strain. Moreover, any risk to animal health from suspension is not as severe nor as important as the human health risk from continued application of these antibiotics in animal feed.

D. The Availability of Other Approaches to Protect the Public Health

The fifth and final criterion for a finding of imminent hazard is the lack of other suitable approaches to protect the public.

We have found no mention in the literature of effective alternatives, or, indeed, any alternatives to protect the public health other than a ban on subtherapeutic uses of penicillin and tetracyclines in animal feed. While the only conceivable possibility would be an extensive public education campaign on careful food and meat handling, this approach presents a number of difficulties. First, developing and implementing a large-scale education program would be more time consuming and less effective than an immediate ban in preventing unneccesary deaths and illness. Second, antibiotic-resistant bacteria, like other bacteria, can be transferred from animals to humans without the humans having direct contact with the animals. Humans can contract bacteria from utensils and kitchen counters that were at one point in contact with the animal or its by-products, such as the raw meat. Therefore, even careful handling of meat would be unlikely to eliminate completely the risk of bacterial transfer

from animals to humans. Finally, a public education program would be expensive and resource-intensive, cancelling out some of the economic arguments against banning subtherapeutic uses of penicillin and tetracyclines in animal feed. NRDC concludes that a public education campaign would be an unsatisfactory option, leaving no alternative but a ban.

CONCLUSION

In conclusion, we believe that (1) there is a very serious public health threat posed by the subtherapeutic use of penicillin and tetracyclines in animal feeds; (2) that the Secretary should act immediately to suspend approval of these uses, pending completion of withdrawal proceedings; and (3) the FDA should proceed expeditiously to complete the withdrawal proceedings it initiated in 1977.

We urge the members of this Committee and others in Congress to support and encourage immediate action by the Secretary of HHS and FDA to protect the public health from this serious threat. These agencies should be allowed to address this problem, unhampered by Congressional constraints. Indeed, Congress should encourage the Secretary to act expeditiously on NRDC's imminent hazard petition and the FDA to proceed immediately with final withdrawal proceedings.

Thank you.

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November 20, 1984

Hon. Margaret M. Heckler
Department of Health and Human
Services
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Dear Secretary Heckler:

The Natural Resources Defense Council, Inc. (NRDC) requests that you act immediately to suspend approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds. On the basis of recent scientific evidence, it is estimated that hundreds of thousands of people are placed at risk and hundreds of human deaths may result each year from such use of these antibiotics.

In 1977, the FDA initiated proceedings to withdraw approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds. The withdrawal procedures, however, were delayed by, among other things, Congressional advice to the FDA to postpone action until more conclusive studies were completed.

Now, recent studies have incontrovertibly shown that a serious public health threat exists. These studies show that (1) widespread use of subtherapeutic doses of penicillin and tetracyclines in animal feeds contributes to the development of bacteria resistant to these drugs; (2) antibiotic-resistant bacteria in animals can be transmitted to humans; and (3) the transmission of strains of bacteria resistant to these antibiotic drugs poses a serious threat to the public health.

In light of these studies, the FDA should renew its efforts to ban such uses of these drugs. In the meantime, you, as Secretary of Health and Human Services, should act immediately to suspend approval of such uses of these drugs because of the imminent hazard to public health.

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The subtherapeutic use of antibiotics in animal feeds has been a major concern of the Natural Resources Defense Council for over a decade. In 1972, in response to a FDA proposed statement of policy,[1] NRDC sent comments to the FDA urging the withdrawal of approvals of subtherapeutic use of antibiotics and sulfonamides in animal feeds. Before Congress, NRDC submitted an extensive statement encouraging passage of H.R. 7285, a bill which would have required FDA to regulate subtherapeutic uses of antibiotics in animal feeds.[2]

When industry petitioned FDA in 1981 to vacate proposed actions that would limit the use of antibiotics in animal feed, NRDC countered with petitions to the contrary.[3] In 1983, NRDC filed extensive comments vigorously opposing FDA's proposed rule that would have allowed new approvals of subtherapeutic use of penicillin and tetracycline in animal feeds for the first time in ten years.[4]

Most recently, on October 22, 1983, NRDC sent President Reagan and you a letter requesting a ban on the subtherapeutic use of penicillin and tetracyclines in livestock feeds. Over 300 scientists supported the requested ban, including some of this country's leading scientists, physicians, and biologists. Since 1979, NRDC's activities in this area have been overseen by its Antibiotic Science Advisory Committee, members of which are all experts in this field. (See attached list.)

NRDC's petition requesting immediate suspension is enclosed. It provides detailed documentation of why suspension should be ordered.

We hope you will give this issue the very serious consideration it deserves and that you will act immediately to suspend approval of subtherapeutic use of penicillin and tetracyclines in animal feeds.

Respectfully submitted,

A. Karim Ahmed, Ph.D.
Senior Staff Scientist

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1 37 Fed. Reg. 2444 (Feb. 1, 1972).

2 See Antibiotics in Animal Feed: Hearing Before the Subcommitee on Health and Environment of the House Comm. on Interstate and Foreign Commerce, 96th Cong., 2nd Sess. 533 (1980).

3 See 48 Fed. Reg. 4554 (Feb. 1, 1983) (denying petitions).

4 48 Fed. Reg. 4490 (Feb. 1, 1983)(proposed rule).

Hon. Margaret M. Heckler
November 20, 1984

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Hon. Margaret M. Heckler
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PETITION

of the

NATURAL RESOURCES DEFENSE COUNCIL, INC.

to the

SECRETARY OF HEALTH AND HUMAN SERVICES

REQUESTING
IMMEDIATE SUSPENSION OF APPROVAL OF THE
SUBTHERAPEUTIC USE OF
PENICILLIN AND TETRACYCLINES
IN ANIMAL FEEDS

November 20, 1984

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The Natural Resources Defense Council, Inc. (NRDC) hereby petitions the Secretary of Health and Human Services to suspend immediately approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds, pursuant to Section 512(e)(1) of the Food, Drug and Cosmetic Act, 21 U.S.C. § 360b(e)(1). This section of law authorizes the Secretary of Health and Human Services to suspend approval of an application for use of a new animal drug if "there is an imminent hazard" to the health of man or of the animals for which the drug is intended.

NRDC submits that an imminent hazard to the public health is posed by the subtherapeutic use of penicillin and tetracyclines in animal feeds. Recent studies have confirmed that (1) widespread use of subtherapeutic dosages of these drugs in animal feeds contributes to the development of bacterial resistance to these drugs and (2) the presence in the environment of strains of resistant bacteria to these antibiotic drugs poses a serious threat to the public health.

In 1977, the FDA initiated withdrawal proceedings with respect to its approval of the use of subtherapeutic doses of penicillin and tetracyclines in animal feeds. The withdrawal procedure was, however, held up by, among other things, Congressional advice to the FDA to postpone action until more conclusive studies were completed.

Recently, newly published studies have conclusively confirmed that a serious public health threat exists. In light of these studies, FDA should renew its efforts to ban subtherapeutic

use of these drugs in animal feeds. In the meantime, suspension of approval, pending completion of administrative proceedings for withdrawal, should be ordered.

I. CRITERIA FOR SUSPENSION

The criteria the Secretary has proposed be used in determining whether an "imminent hazard" exists and, consequently, whether approval of a drug application should be suspended pending withdrawal proceedings are:

(A) The likelihood that, after the customary administrative process is completed, the product will be withdrawn from the market;

(B) The severity of the harm that could be caused by the product during the completion of customary administrative proceedings to withdraw the product from the market;

(C) The likelihood that the product will cause such harm while the administrative process is being completed;

(D) The risk to the health of humans or animals currently taking the product that might be occasioned by the immediate removal of the product from the market, taking into account the availability of alternatives to the product and the steps necessary for affected persons to adjust to these other alternatives; and

(E) The availability of other approaches to protect the public health.

44 Fed. Reg. 48,979 (to be codified at 21 C.F.R. §2.1) (proposed August 21, 1979) (proposed rule establishing imminent hazard criteria and procedure).

Similar criteria were employed by then-Secretary Joseph Califano in suspending approval of new human drug applications for phenformin hydrochloride. Order of the Secretary Suspending Approval, New Drug Application for Phenformin (July 25, 1977).

These criteria were upheld in the face of legal challenge. The district court for the District of Columbia, refusing to enjoin enforcement of the Phenformin suspension order, held that the Secretary's criteria properly reflected Congressional intent as to imminent hazard. Forsham v. Califano, 442 F. Supp. 203 (D.D.C. 1977), dismissed as moot per curiam, No. 77-1478 (D.C. Cir. 1979). The district court expressed approval of the Secretary's interpretation of imminent hazard, stating:

> [W]e are not inclined to adopt plaintiff's "crisis" interpretation of imminent hazard. Rather we are more persuaded by defendant's suggested analogy to cases interpreting the imminent hazard provisions of the Federal Insecticide, Fungicide and Rodenticide Act which caution "against any approach to the term imminent hazard...that restricts it to a concept of crisis" and adopt the view that "It is enough that there is substantial likelihood that serious harm will be experienced during any realistic projection of the administrative process." See Environmental Defense Fund v. EPA, 510 F.2d 1292, 1297 (1975); Environmental Defense Fund v. EPA, 465 F.2d 528, 540 (1972).

Id. at 208.

To justify invocation of the imminent hazard provision, what must be shown is that there is a substantial likelihood that serious harm would occur pending completion of normal administrative proceedings. The harm need not be immediate. Rather, consideration of the seriousness of the harm extends to "long-term effects that may be initiated during that period, the final anticipated injury from which occurs later." 44 Fed. Reg. at 48,981. The development of antibiotic-resistant strains of bacteria is just such a long-term effect. It is closely analogous to the long-term environmental contamination and carcinogenic risks caused by certain pesticides summarily suspended under the imminent hazard provision of the Federal

Insecticide, Fungicide and Rodenticide Act ("FIFRA"), 7 U.S.C. §136d(c). Several cases approving the application of the imminent hazard provision of that act, e.g., Environmental Defense Fund v. EPA, 510 F.2d 1292 (D.C. Cir. 1975) (aldrin/dieldrin), Environmental Defense Fund v. EPA, 548 F.2d 998 (D.C. Cir. 1976), cert. denied, 431 U.S. 925 (1977) (heptachlor/chlordane), are discussed as precedent in Secretary Califano's Order on phenformin and the proposed rule (44 Fed. Reg. at 48,981).

NRDC submits that the criteria for invoking the "imminent hazard" provision of the Food, Drug and Cosmetic Act, 21 U.S.C. § 360b(e)(1), have been met with respect to the subtherapeutic use of penicillin and tetracyclines in animal feeds. The reasons are set forth below.

II. APPLICATION OF CRITERIA

A. Likelihood of Withdrawal

The first criterion to be used in deciding whether an imminent hazard exists is the likelihood that FDA approval of the drug application will be withdrawn. 44 Fed. Reg. at 48,982. Section 360b(e)(1)(B) requires the FDA to withdraw approval of a new animal drug application when new evidence shows that the drug is not shown to be safe. Because new evidence clearly demonstrates that subtherapeutic use of penicillin and tetracyclines in animal feeds is not shown to be safe, there is a substantial likelihood that the FDA will withdraw its approval.

Indeed, in 1977, based on numerous studies demonstrating the health hazards associated with the subtherapeutic use of penicillin and tetracyclines in animal feeds, the FDA concluded that such use of these antibiotics had not been shown to be safe and proposed to withdraw its approval for such uses. 42 Fed. Reg. 43,772 (Aug. 30, 1977) (penicillin); 42 Fed. Reg. 56,264 (Oct. 21, 1977) (tetracyclines). Since 1977, additional scientific evidence has been gathered which demonstrates overwhelmingly the need for withdrawal.

1. FDA Proposed Withdrawal and Findings, 1977

In 1977, based on data it had collected from independent studies and from the drug industry, the FDA found that the use of penicillin and tetracyclines in animal feeds posed a serious human health threat and initiated withdrawal proceedings. The Director of the FDA's Bureau of Veterinary Medicine (now the Center for Veterinary Medicine) presented a detailed analysis of the scientific evidence with respect to penicillin in the notice of opportunity for hearing. 42 Fed. Reg. 43,772 (August 30, 1977). In the summary, the Director concluded:

> Evidence demonstrates that the use of subtherapeutic levels of penicillin and other antibiotics in animal feed contributes to the increase in antibiotic resistant E. coli and in the subsequent transfer of this resistance to Salmonella. Further, many strains of E. Coli and Salmonella infect both man and animals.
>
> The holders of approved NADA's have submitted no evidence to demonstrate that the observed strains of E. Coli and Salmonella in man and animals are mutually exclusive; in fact, the evidence is overwhelming to the contrary. Furthermore, in some cases the R-plasmids as well as the resistance genes from human and animal sources are indistinguishable. Thus, the potential for harm exists, as illustrated by the studies submitted and verified by evidence

> from studies conducted by independent scientists. No evidence has been submitted by any NADA holder to resolve conclusively the safety questions raised by this potential...

42 Fed. Reg. at 43,775.

The Director concluded that subtherapeutic use of penicillin creates a selective pressure on bacteria in animals to develop strains resistant to penicllin and related anti-bacterial drugs. 42 Fed. Reg. at 43,776. These bacteria, present in the animals' systems, are released into the human environment, either through direct contact of humans with farm animal or their feces, or more likely through the presence of the bacteria in animal and dairy food products. 42 Fed. Reg. at 43,776-7.

The Director was further concerned that subtherapeutic use of penicillin in animal feeds might compromise the treatment of animal diseases with antibiotics. 42 Fed. Reg. at 43,787-8. The Director found that studies submitted by industry did not alleviate this concern or show the drug to be safe.

The Director found that subtherapeutic uses of tetracyclines in animal feeds produce effects similar to those produced by penicillin. 42 Fed. Reg. 56,264. The findings as to tetracycline are based on much of the same evidence as, and are substantially similar to those for penicillin. On the basis of these findings, FDA proposed to withdraw approval of most subtherapeutic uses of tetracyclines in animal feeds.

Neither the proposed withdrawal for penicillin nor tetracyclines became final.

2. Recent Scientific Evidence, 1982-1984

(a) O'Brien et al. Study

In 1982, Dr. Thomas O'Brien and his associates at Harvard Medical School reported a study of antibiotic-resistant Salmonella bacteria (Salmonella typhimurium var. copenhagen) taken from people and food animals in several states in the United States.[1] This study isolated from the bacteria the pieces of non-chromosomal genetic material called plasmids which carry antibiotic resistance. Using a new biochemical technique to analyze the plasmids' DNA structure, the O'Brien study could identify related bacterial strains by comparing DNA fragments from plasmids in different bacteria in a variety of host organisms.

The O'Brien study found that plasmids from bacteria obtained from humans were genetically related to plasmids in bacteria isolated from animals. In fact, certain plasmids found in bacteria in human and animals were virtually identical. The similarity between the strain of bacteria and its plasmids from humans and animals in this study provides very strong evidence that antibiotic-resistant bacteria are transmitted between animals and humans on a widespread basis.

The above study also found similar or identical plasmid in bacteria from humans in widely-dispersed geographic locations. They were all identical to a plasmid carried by a single widely dispersed Salmonella strain in animals. The appearance of

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1 O'Brien, et al., Molecular Epidemiology of Antibiotic Resistance in Salmonella from Animals and Human Beings in the United States, 307 New Eng. J. Med. 1 (1982).

similar plasmids in human bacteria in a variety of places among persons having no direct contact with food animals is strong support for the contention that these antibiotic-resistant bacteria are being transmitted from animals to humans through the food chain. The above finding can only be explained by multiple independent incidents of transfer of antibiotic-resistant strain Salmonella from animals to humans.

(b) Holmberg et al. Study

In 1983, Dr. Scott Holmberg and his associates from the Centers for Disease Control in Atlanta conducted a study of 18 patients from four midwestern states who had contracted infections of Salmonella newport with identical plasmid profiles and multiple antibiotic resistance.[2] Holmberg and his associates concluded that the source of the Salmonella bacteria of all 18 patients was a single beef herd in South Dakota. The only human (six-state area) or animal (United States) isolate of this strain of Salmonella newport in the year before the outbreaks was from dairy cows on a South Dakota farm adjacent to a feedlot beef farm. Several of the 18 persons studied were known to have consumed beef directly from the herd and epidemiological evidence based on the distribution of the meat indicated that other patients also consumed beef which originated from the single feedlot beef farm. The beef herd had been fed subtherapeutic levels of chlortetracycline for over a year before the first human subject became ill.

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2 Holmberg, et al., Drug-Resistant Salmonella from Animals Fed Antimicrobials, 311 New Eng. J. Med. 617 (1984).

The Holmberg study has extraordinary significance for illustrating the risk to human health from the use of antimicrobials in animal feed. This is the first definitive study to directly link subtherapeutic use of antibiotics in animals to human disease and death (one of the 18 subjects in Holmberg's study died from Salmonella infection). The Holmberg study demonstrates that antimicrobial-resistant bacteria in animals can be transmitted to and colonize in humans. Before now, this contention was probably the most disputed of all the steps involved in establishing the human health risks associated with the feeding of antimicrobials to animals. 42 Fed. Reg. at 43,776.

Another important finding of the Holmberg study is the observation that many patients had been taking antibiotics for treatment of minor infections a few days prior to being hospitalized for salmonellosis. It is well-known that antibiotics can facilitate infection with resistant organisms because they inhibit sensitive bacterial flora of the host, enabling the invading resistant strains to gain a foothold and proliferate. Thus, individuals who harbor asymtomatic infection from antibiotic-resistant bacteria are at higher risk of gastrointestinal infection, since antibiotics are used commonly in therapeutic treatment for a variety of bacterial infections in the general population.

(c) Holmberg, Wells and Cohen Study

In a recently published paper,[3] Holmberg, Wells and Cohen of the Centers for Disease Control examined the origin and severity of antibiotic-resistant strains of bacteria responsible for 52 reported Salmonella outbreaks over a 12-year period. They report that multiple drug-resistant isolates have accounted for a steadily increasing percentage of human Salmonella infections and now represent approximately 20 to 30 percent of identified cases.[4] Because the increase of resistant bacteria is rapidly diminishing the effectiveness of doses for human use, there is a greater urgency for action to halt the proliferation of resistant bacteria. They reported, on the basis of epidemiological investigation, that of the 38 outbreaks of Salmonella infection from an identified source or mode of transmission, 69% of the resistant strains and 38% of the sensitive strains were of food-producing animal origin. The study also found that "[t]he case fatality rate for patients with identified infections with multiply resistant Salmonella was 4.2 percent, 21 times higher than the case fatality rate associated with antimicrobial-sensitive Salmonella infections."[5] The conjunction of the mortality rate for persons suffering from resistant Salmonella with the increasing frequency of resistant Salmonella make it urgent that action be taken to abate the spread of resistant bacteria.

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3 Holmberg, Wells and Cohen, Animal-to-Man Transmission of Antimicrobial-Resistant Salmonella: Investigations of U.S Outbreaks, 1971-1983, 225 Science 833 (1984).

4 Id.

5 Id.

3. Conclusion

There is overwhelming evidence to support withdrawal of subtherapeutic uses of penicillin and tetracyclines in animal feed. Therefore, the first criterion of suspension, the likelihood of withdrawal, is met.

B. Severity of Harm

The second criterion to be used in determining whether use of a drug constitutes an imminent hazard is the severity of the harm that could be caused by the product pending the completion of customary administrative proceedings to withdraw the product from the market.

On the basis of recent scientific evidence it can be established that hundreds of human deaths each year and several hundred deaths prior to the completion of withdrawal proceedings could result from subtherapeutic use of penicillin and the tetracyclines in animal feed.

It has been known for some time that subtherapeutic use of penicillin and tetracyclines in animal feed exerts selective pressure on animal bacterial populations, creating large reservoirs of strains of bacteria resistant to these and closely related antibiotics.[6] Salmonella bacteria resistant to one or more antibiotics are responsible for the majority of human deaths

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6 Sun, M., Use of Antibiotics in Animal Feed Challenged, 226 Science 144 (1984).

from Salmonella infection.[7] Dr. Holmberg's recent study shows that 69% of all multiply resistant Salmonella outbreaks in humans are traceable to animal sources, either animal-source food or live animals.[8] Given the selective pressure for the proliferation of resistant strains cited before, these findings clearly implicate subtherapeutic use of antibiotics in animal feed with human disease. In the discussion of likelihood of harm which follows, we discuss the number of deaths which could be associated with continued subtherapeutic use of these antibiotics in animal feed pending completion of withdrawal proceedings.

The less severe harm associated with nonfatal cases of infection with antibiotic-resistant strains of Salmonella should also be weighed in the imminent hazard determination. The resistance to antibiotics in these cases results in difficulty of treatment when indicated and consequently in longer duration of the illness and its symptoms. Further, there is evidence that treatment of other diseases with antibiotics may cause resistant Salmonella to predominate in an individual's system and result in the symptomatic expression of an otherwise asymptomatic infection.[9]

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7 Holmberg, supra, p. 10, 225 Science at 835.

8 Id. at 834.

9 Holmberg, supra p. 8, 311 New Eng. J. Med. 617.

C. Likelihood of Harm

The third component of the imminent hazard determination is the likelihood that the product will cause serious harm while the administrative process is being completed. The administrative process of withdrawal of the new animal drug approvals of penicillin and tetracyclines has already taken several years. Completion of this administrative process could take another three years.[10]

A preliminary risk analysis, outlined below, projects a mortality rate of between 100 and 300 deaths per year linked to subtherapeutic animal feed uses of penicillin and tetracyclines. In addition, over 2,700 reports of Salmonella cases and over 270,000 unreported cases of Salmonella infection may be associated on an annual basis with the use of penicillin and tetracyclines in animal feeds. These data demonstrate that there is a substantial likelihood of serious harm to the public health being caused while withdrawal proceedings are completed.

1. Estimated Annual Mortality Linked to Animals Fed Subtherapeutic Doses of Penicillin and Tetracyclines in Animal Feed

(a) Method 1

According to the Centers for Disease Control, approximately 40,000 cases of Salmonella infection in humans are reported each

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10 Letter from Alair Townsend, Assistant Secretary for Management and Budget, HHS, to Hon. Jamie I. Whitten, Chairman, House Committee on Appropriations (June 23, 1981).

year in the United States.[11] Since 20-30% of Salmonella strains isolated from humans are resistant to one or more antibiotics,[12] a conservative estimate of the number of cases due to resistant strains of Salmonella bacteria is 8,000 (20%). Of these, an estimated 336 cases may be fatal, assuming a 4.2% fatality rate ror resistant Salmonella infections.[13] Since 69% of reported Salmonella outbreaks involving antibiotic-resistant strains are traceable to animal sources, of the estimated 336 deaths from resistant bacteria 69%, or 232, are attributable to resistant bacteria from animal sources. Penicillin and tetracyclines constitute approximately 50% of all antibiotics produced in the United States.[14] We can assume that a similar proportion of penicillin and tetracyclines is used in the livestock industry (although the percentage may in fact be higher) since approximately half the antibiotics produced in the United States is

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11 Personal communication with Scott D. Holmberg, M.D., Enteric Diseases Branch, Centers for Disease Control, Atlanta, Georgia. This estimate is supported by the figure of 35,625 cases reported in 1981, up 10,000 from ten years earlier, reported by Riley, Importance of Host Factors in Human Salmonellosis Caused by Multiresistant Strains of Salmonella, 149 J. of Infectious Diseases at 878 (1980).

12 Holmberg, supra p.10, 225 Science at 833.

13 Id.

14 Personal communication with Edward Capeuchelli, Energy and Chemical Division, U.S. Trade Commission, Washington, D.C. In 1982, penicillin (9,507,000 lbs) and tetracycline (7,243,000 lbs) accounted for a total of 51.5% of the 32,518,000 lbs. of antibiotics produced in the U.S.

used in the animal livestock industry.[15] Next, since subtherapeutic antibiotic use constitutes most of all antibiotic use for animals, we assume that this use is responsible for virtually all antibiotic resistance among animal bacterial populations.[16] Thus, if half the resistant strains of Salmonella from animal sources have emerged under the selective pressure of subtherapeutic use of penicillin and tetracyclines, it is estimated that 116 (0.5 x 232) Salmonella deaths each year are associated with subtherapeutic use of these antibiotics.

(b) Method 2

An alternative method of risk estimate is based on the actual mortality incidence from Salmonella infections. According to statistics compiled by the Centers for Disease Control, between 1,000 and 1,500 deaths each year are associated with Salmonella outbreaks in the United States.[17] The recent Holmberg, et al., study indicates that 76.5% of all fatal

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15 National Academy of Sciences, The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds 7-8 (1980).

16 The remaining use of antibiotics in animals is for therapeutic treatment which is episodic in nature and of limited duration. It is reasonable to assume that such use does not contribute significantly, if at all, to the longterm, sustained development of antibiotic-resistant bacterial strains in animals.

17 Private communication with Scott D. Holmberg, M.D., Enteric Diseases Branch, Centers for Disease Control, Atlanta, Ga.

Salmonella infections are associated with resistant bacteria.[18] Application of this percentage to the lower estimate of 1,000 Salmonella fatalities per year gives an estimate of 756 deaths per year from resistant strains of Salmonella. As in the first method of analysis, the number of fatal resistant infections traceable to animal sources is estimated based on the finding that 69% of multiply resistant Salmonella outbreaks are traceable to animal sources, giving a figure of 528 deaths per year. As in the previous analysis, it is assumed that penicillin and tetracyclines constitute 50% of the antibiotics used subtherapeutically in animal feed and that virtually all antibiotic-resistant strains of Salmonella of animal origin are linked to subtherapeutic use of antibiotics in animal feed. Thus, an estimated one-half of the 528 fatalities from infections by resistant strains result from subtherapeutic use of penicillin and tetracyclines, or 264 deaths per year.

2. Estimated Annual Morbidity Linked to Animals Fed Subtherapeutic Doses of Penicillin and Tetracyclines in Animal Feed

Resistant strains of bacteria emerging in animal populations given subtherapeutic amounts of penicillin and tetracyclines in animal feed could be responsible for an estimated 270,000 nonfatal cases of Salmonella each year. In these 270,000 cases the

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18 Holmberg, supra p. 10, 225 Science 833-834. Holmberg found 13 deaths from 312 Salmonella cases associated with resistant bacteria and 4 deaths from 1,912 Salmonella cases associated with sensitive strains. Thus, out of a total of 2,224 cases, 13 out of 17 deaths, or 76.5% were associated with resistant Salmonella strains.

resistance of the bacteria to antibiotic treatment may increase the duration of the illness and its symptoms. This estimate is arrived at by means of the following analysis. Approximately 40,000 cases of Salmonella bacterial infection are reported each year.[19] An estimated 20% of these cases, or 8,000 cases, are infections by resistant strains of bacteria.[20] Of these estimated 8,000 reported cases of infection by resistant Salmonella, 69%, or 5,520, can be attributed to animal sources, and 50% or 2,760, of these are attributed to bacterial strains whose resistance is a result of subtherapeutic use of penicillin and tetracyclines in animal feeds.[21] Since only approximately 1% of all cases of Salmonella infection are clinically reported,[22] the 2,760 figure is multiplied by one hundred, giving an estimate of over 270,000 cases of non-fatal salmonellosis each year due to strains whose resistance is associated with the subtherapeutic use of penicillin and tetracyclines in animal feeds.

D. Risk To Human or Animal Health of Suspending Subtherapeutic Uses of Penicillin and Tetracyclines in Animal Feeds

The fourth criterion used in deciding whether an imminent hazard exists is the risk to the health of humans or animals that would result from the immediate removal of the drug. No significant risk would be associated with suspending approval of

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19 Supra, p. 13.

20 Supra, p. 14.

21 Id.

22 Private communication with Scott D. Holmberg, M.D., Enteric Branch, Centers for Disease Control, Atlanta, GA.

subtherapeutic uses of penicillin and tetracyclines in animal feed. No potential health risks to humans have been discussed in the literature. The health risk to animals can be greatly minimized, or even eliminated, by use of substitute antibiotics and better farming practices.

1. Risks to Animal Health

It has been claimed that subtherapeutic doses of antibiotics are fed to farm animals in order to (1) prevent disease outbreaks among livestock, (2) increase feed efficiency (weight gain per unit of food) and (3) promote growth.[23]

Withdrawing subtherapeutic uses of penicillin and tetracyclines would serve to eliminate these intended benefits. Decreased feed efficiency and slower growth are purely economic effects. They pose no health risks to the animals. The sole health risk to animals, then, is the hypothetical increased likelihood of disease. This risk is not severe, since diseased animals, whether or not they are already receiving low levels of antibiotics, are typically treated with therapeutic doses of antibiotics. NRDC is not advocating a ban on treatment of actual disease with antibiotics. Additionally, it is increasingly recognized by the livestock industry that antibiotics at any dose level do not treat infection caused by resistant organisms.

Two effective alternatives exist to minimize the incidence of illness among farm animals. The first and simplest alterna-

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23 Office of Technology Assessment, U.S. Congress, Drugs in Livestock Feed, Vol. I: Technical Rept. 5 (1979).

tive is for farmers to substitute other antibiotics for penicillin and tetracyclines in animal feeds. Alternative antibiotics currently used in animal feeds include bacitracin, nitrofurazone, banbermycin, novobiocin, monensin, tylosin and others.[24]

Though some have argued that the substitutes for penicillin and tetracyclines are not as effective, there is substantial evidence that they are effective. For example, tylosin and bacitracin are considered excellent substitutes for tetracyclines and penicillin in swine, chicken and turkeys.[25] In the case of pork and beef, tylosin and bacitracin are considered viable substitutes.[26]

Another method of reducing the incidence of disease in farm animals would involve altering farming practices. Intensive farming practice confines animals, usually with very little room for each animal, for most or all of their lives, and rigidly controls their diet, thereby altering their physical and behavioral characteristics. The confinement and crowding creates a great deal of stress for animals, and this stress increases the risk of disease. Since the animals are so crowded, disease spreads quickly. Many farmers who practice this type of animal

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24 Report of the Comptroller General of the United States, U.S. General Accounting Office: Need To Establish Safety And Effectiveness of Antibiotics Used In Animal Feeds 4 (1977). Haysten, I. et al., Effect of Banbermycin and Tylosin on Performance of Growing-Finishing Swine, 50 J. Animal Sciences 484 (1980).

25 Headley, J.C., Economic Aspects of Drug and Chemical Additives, p. 30, paper commissioned for OTA study, supra, p. 18.

26 Id.

husbandry may feel that it is necessary to administer subtherapeutic doses of antibiotics in order to counteract these disease-producing and disease-spreading influences. Even so, death losses have increased due to confinement systems, at least in hog farming,[27] and this can often be attributed to bacterial resistance to antibiotics being used in a futile attempt to control infections.

Non-intensively farmed animals are not confined as much, may have access to the outdoors and are weaned later. Each of these practices lessens the stress on the animals. This type of farming is relatively low cost, since the farmer need not buy the expensive facilities and equipment needed by the confinement farmer.[28]

Finally, unsanitary conditions cause the animals to be even more stressed, and antibiotic need is, therefore, greater. Only a small number of farms may actually have these conditions, but there is concern that some use of antibiotics may be covering up for bad practices.[29] In these cases, better sanitation could minimize the animal health risk posed by removal of antibiotics.

For farms with less intensive animal-raising practices and good management, subtherapeutic levels of antibiotics may not be

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27 Statement of Charles Henry Hassebrook, Center for Rural Affairs, Walthill, Nebraska, before the House Committee on Interstate and Foreign Commerce, Subcommittee on Health and the Environment, Serial No. 96-169, June 12 and 24, 1980.

28 Id.

29 Green, Feed Additives: A Crutch for Poor Management? Feedstuffs, Feb. 18, 1980, 36.

necessary. If they can still decrease the extent of disease, then effective substitutes for penicillin and tetracyclines are available. NRDC is, therefore, convinced that there is no significant health risk to animals associated with banning subtherapeutic doses of penicillin and tetracyclines from animal feed. On the contrary, there is a positive benefit, since if the animals should become ill, there is at least the chance of treating them if the causative agent is a sensitive bacterial strain.

In conclusion, the risk to animal health from suspension is not as severe nor as important as the human health risk from continued application of these antibiotics in animal feed.

2. Risks To Human Health

NRDC has found no evidence or even suggestions in the medical and public health literature that withdrawal of penicillin and tetracyclines from subtherapeutic uses in animal feeds would result in risks to human health. The only effect on humans would be economic. A number of studies have modelled production and prices of meat if various combinations of antibiotics are banned from animal feed. Results indicate that economic losses to consumers will be felt mostly in the first few

years of a ban[30] and that, over the longer term, use of existing alternatives to these antibiotics would substantially mitigate the economic effects on consumers.[31]

Since the average citizen consumes almost three times the amount of meat per year that the U.S. Department of Agriculture considers necessary to meet nutritional standards,[32] the difference of a few less pounds of meat or a few extra dollars per year per person cannot be considered a human health risk. Economic hardship may be felt by the low-income members of society, but no evidence suggests that this presents a health problem, given the fact that most food prices will not be affected by a ban, and the impact of slightly nigher meat prices is, for the most part, temporary.

A conceivable risk to human health could be that of eating meat from an animal which became ill as a result of withdrawing subtherapeutic use of penicillin and tetracyclines. First, using alternate antibiotics and improved farming practices, a farmer can control disease in the great majority of animals. If an animal does become ill, the farmer can treat the animal with therapeutic doses of antibiotics, a standard practice whose effectiveness would actually be increased by the proposed ban.

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30 U.S. Dept. of Agriculture, Economic Effects of a Prohibition on the Use of Selected Animal Drugs 2 (1978).

31 Headley, supra p. 19, at 30-31.

32 Council for Agricultural Science and Technology, Antibiotics in Animal Feeds 34 (1981).

E. The Availability of Other Approaches to Protect the Public Health

The fifth and final criterion for a finding of imminent hazard is the lack of other suitable approaches to protect the public.

NRDC has found no mention in the literature of effective alternatives, or, indeed, any alternatives to protect the public health other than a ban on subtherapeutic uses of penicillin and tetracyclines in animal feed. While the only conceivable possibility would be an extensive public education campaign on careful food and meat handling, this approach presents a number of difficulties. First, developing and implementing a large-scale education program would be more time consuming and less effective than an immediate ban in preventing unnecesary deaths and illness. Second, antibiotic-resistant bacteria, like other bacteria, can be transferred from animals to humans without the humans having direct contact with the animals. Humans can contract bacteria from utensils and kitchen counters that were at one point in contact with the animal or its by-products, such as the raw meat. Therefore, even careful handling of meat would be unlikely to eliminate completely the risk of bacterial transfer from animals to humans. Finally, a public education program would be expensive and resource-intensive, cancelling out some of the economic arguments against banning subtherapeutic uses of penicillin and tetracyclines in animal feed. NRDC concludes that a public education campaign would be an unsatisfactory option, leaving no alternative to a ban.

III. CONCLUSION

In view of the likelihood that FDA will utlimately withdraw approval, the severe harm that is likely to occur pending completion of withdrawal proceedings, the insignificant risk to human or animal health from suspension and the lack of effective alternatives to protect the public health, NRDC respectfully requests that you act immediately to suspend approval of subtherapeutic use of penicillin and tetracyclines in animal feeds.

Respectfully submitted,

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Prepared with the assistance
of Susan Grunes, Legal Intern
and Lisa Aronson, Science Intern

The undersigned certify that, to the best of their knowledge and belief, this petition includes all data and information on which the petition relies, and that it includes representative data and information known to the petitioners that are unfavorable to the petition.

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Mr. GORE. Thank you very much.

Our third witness is Dr. Wes Bonner, with the National Cattlemen's Association in Englewood, CO. Dr. Bonner, we're delighted to have you here. Please proceed.

[The biographical sketch of Dr. Bonner follows:]

BIOGRAPHICAL SKETCH

Wesley Bonner, D.V.M.

Dr. Wesley Bonner is a licensed veterinarian with federal accreditation and thirteen years of experience in bovine medicine. He graduated from Texas A & M University in 1969 with a D.V.M. degree.

Dr. Bonner is a member of the American Veterinary Medical Association, Texas Veterinary Medicine Association, American Association of Bovine Practitioners and the Academy of Veterinary Consultants. He has served on the Board of Directors and has been a committee chairman for the Texas Cattle Feeders Association and is currently chairman of the Task Force on Antibiotics Policy for the National Cattlemen's Association. Dr. Bonner is a long-standing member of the Animal Health and Identification Committee of NCA and currently serves as Chairman of NCA's Subcommittee on Animal Drugs, Biologics and Feed Additives.

Prior to practicing veterinary medicine, Dr. Bonner was a researcher at Woodruff medical Center at Emery University in Atlanta, Georgia from 1969-1971.

Currently, Wesley Bonner is part owner and general manager of a 12,000-head feedyard near Veribest, Texas. He also is part owner of a grain elevator and is involved in the cattle ranching business near Veribest.

Dr. BONNER. Mr. Chairman, a country boy always enjoys the opportunity to come to town. However, I don't want to confuse the educational and democratic process of this hearing with the Cowboys Saturday night. [Laughter.]

My name is Wes Bonner. I am a veterinarian from Veribest, TX. I am part owner of a commercial cattle feedyard and I am here today representing the National Cattlemen's Association as chairman of its special antibiotic task force.

For the record, beef cattle producers and feeders make very limited use of the tetracyclines at low levels in feeds fed on a continuous basis for growth promotion and feed efficiency. No use is made of penicillin as a feed additive for beef cattle. Most cattle feeders who use feed additives have opted to use, as previously discussed, instead of tetracyclines, the products known as ionophores, namely monensin and lasalocid.

If I may further cloud the issue, in a recent publication by Dr. James Steele, who is a retired Assistant Surgeon General—he documented that 42 percent of the antibiotics produced in this country are consumed by humans; 48 percent by animals; and 10 percent in other environmental uses.

That 25 percent of the tetracyclines are used in people; 75 percent in animals, but the level consumed in humans is 27 times greater than that in animals, making a therapeutic 4-day level for every human in the United States.

The National Cattlemen's Association is concerned about the prospect of a ban or restriction on the use of penicillin and tetracyclines, in part because we have questions about the objectivity of the Food and Drug Administration. If a precedent is set whereby

animal health products can be removed from the market without sufficient scientific justification, livestock producers will not be able to depend on the future availability of helpful products. Such a possibility of biased decisionmaking is not beyond imagination.

In 1977, the FDA Commissioner, Donald Kennedy, ignored the recommendations of the National Science Advisory and Drug Committee and proposed that a ban or restriction be placed on the use of antibiotics in animal feed. He cited "personal and philosophical" reasons for his position. We want to be certain that such personal and philosophical convictions do not form the basis of any decision to ban or restrict the use of these products now.

Political rhetoric cannot be allowed to override sound scientific data and judgment. The question of antibiotic safety must be addressed purely from a public health viewpoint. While it cannot be denied that the final decision will have economic and social impacts, these are not the critical questions. Public health, from our viewpoint, involves both human and animal health. A supply of wholesome and nutritious products available to the consumer in this country has contributed immeasurably to the excellent health of Americans. This could not be possible without healthy animals. This is one example of how human and animal health are inseparable.

More important to the issue at hand is the fact that animals and humans coexist in the same environment. Diseases which affect animals also affect humans in some instances.

In discussions of the public health effects of feed antibiotic use, it would be inappropriate to ignore the benefits which accrue from their use, all economic benefits aside. For example, the instance of occupational disease among people working directly in food animal production and processing has declined over the period of time in which antibiotics have been used in farm animals. This fact is noted by Steele in the "Handbook Series on Zoonosis, Section D: Antibiotics, Sulfonamids and Public Health." It is naive, perhaps, to assume that this decline in occupational disease is due entirely to healthier animals resulting from the use of antimicrobials. However, to ignore such data and to assume that such a relationship cannot exist is equally naive and irresponsible.

The library of information on the subject of antibiotic safety is huge. There are those who would have us believe that the decision to ban the low-level feeding of penicillin and tetracyclines should have been made years ago. However, the National Academy of Sciences published an extensive review of the literature in 1980 and concluded that the postulated hazards of the continued use of antibiotic feeding could, at that time, neither be proven nor disproven.

If evidence has accumulated since that time, it should be weighed on the same scale as the previous reports. This requires a rational approach, and frankly, we have not seen evidence of that.

This is disturbing. The advocates of a ban are still vocal and in their determination to accomplish have chosen to ignore the larger body of evidence in favor of a small number of reports and editorials in which an excessive amount of editorial license was exercised. For instance, at the same time the CDC report was being summarized by media persons throughout the country, and at the same time that certain Members of Congress were proposing legis-

lation as an overreaction to the CDC report, a few scientists were studying the recent report in the October Journal of Clinical Microbiology by Atkinson and Lorian who tested the resistance of nearly 6 million bacterial strains to commonly used antibiotics in hospitals across the United States. They concluded that bacterial susceptibility to antibiotics on a national scale has remained virtually unchanged during the last decade.

We are not suggesting that the paper by Atkinson and Lorian is the final answer; nor should we pretend that the paper by Holmberg, Dr. Cohen, and others, is the final solution. The point is, over 6,000 scientific papers have been published on the subject of bacterial resistance since 1971 in the English language alone. Hopefully, the answers to some of the pertinent questions can be derived from all of this work. It would be irresponsible to move hastily without a review of the science.

Further, with regard to public health, some consideration must be given to the tradeoff which could occur between the therapeutic and subtherapeutic uses of antibiotics, especially penicillin and tetracyclines. It is not inconceivable that, should the instance of clinical morbidity increase in the absence of subtherapeutic antibiotic use, more animals would require therapeutic treatment, which may result in more total antibiotic use. As we talked about earlier, this is unknown.

It is known that therapeutic use of antibiotics also contributes to the reservoir of resistant bacteria. Therapeutic use in animals is small, especially compared to such use in human medicine. Still, it is estimated that the veterinary use of therapeutic doses of penicillin and tetracyclines is only 20 percent as great as such use in human medicine.

In summary, so that there is no misunderstanding, the National Cattlemen's Association recognizes that there is an important scientific debate on the issue of antibiotic safety. We are here neither to defend nor condemn the use of feed grade penicillin and tetracyclines in livestock and poultry production. Our objective is merely to stress the importance of basing every decision on the best scientific information available.

I respectfully submit our comments.

[The prepared statement of Dr. Bonner follows:]

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STATEMENT
of the
NATIONAL CATTLEMEN'S ASSOCIATION

Before the
Subcommittee on Investigation and Oversight of the
Committee on Science and Technology

U.S. House of Representatives

Relative to
The Use of Antimicrobials in Food Animal Production

Presented by:

Dr. Wesley Bonner
Chairman
NCA Task Force on Antibiotics Policy

December 18, 1984

The National Cattlemen's Association is the national spokesman for all segments of the nations's beef cattle industry --- including cattle breeders, producers, and feeders. The NCA represents approximately 245,000 professional cattlemen throughout the country. Membership includes individual members as well as 50 affiliated state cattle associations and 19 affiliated national breed organizations.

INTRODUCTION

For the record, beef cattle producers and feeders make very limited use of the tetracyclines at low levels in feeds, fed on a continuous basis, for growth promotion and feed efficiency. No use is made of penicillin as a feed additive for beef cattle. Most cattle feeders who use feed additives have opted to use, instead of tetracyclines, products known as ionophores (monensin and lasalocid) which have been shown to improve feed efficiency and, in the case of lasalocid, also improve growth rate. However, the National Cattlemen's Association is concerned about the prospect of a ban or restriction on the use of penicillin and tetracyclines in part because we have questions about the objectivity of the Food and Drug Administration. If a precedent is set whereby animal health products can be removed from the market without sufficient scientific justification, livestock producers will not be able to depend on the future availability of helpful products.

Such a possibility (of biased decision-making) is not beyond imagination. In 1977 the FDA Commissioner, Donald Kennedy, ignored the recommendations of the National Advisory Food and Drug Committee and proposed that a ban or restriction be placed on the use of antibiotics in animal feed. He cited "personal and philosophical" reasons for his position. We want to be certain that such "personal and philosophical" convictions do not form the basis of any decision to ban or restrict the use of these products now.

PUBLIC HEALTH

Political rhetoric cannot be allowed to override sound scientific data and judgement. The question of antibiotic safety must be addressed purely from a public health viewpoint. While it cannot be denied that the final decision will have economic and social impacts, these are not the critical questions. Public health, from our viewpoint, involves both human and animal health. The supply of wholesome and nutritious animal products, available to the consumer in this country, has contributed immeasurably to the excellent health of Americans. This would not be possible without healthy animals. This is one example of how human and animal health are inseparable.

More important to the issue at hand is the fact that humans and animals co-exist in the same environment. Diseases which affect animals also affect humans, in some instances. In discussions of the public health effects of feed antibiotic use, it would be inappropriate to ignore the benefits which accrue from their use---all economic benefits aside. For example, the incidence of occupational disease among people working directly in food animal production and processing has declined over the period of time in which antibiotics have been used in farm animals. This fact is noted by Steele in the Handbook Series on Zoonosis, Section D: Antibiotics, Sulfonamids and Public Health. It is naive, perhaps to assume that this decline in occupational disease is due entirely to healthier animals resulting from the use of antimicrobials. However, to ignore such data, and to assume that such a relationship cannot exist, is equally naive and irresponsible.

The library of information on the subject of antibiotic safety is huge. There are those who would have us believe that the decision to ban the low-level feeding of penicillin and tetracyclines should have been made years ago. However, the National Academy of Sciences published an extensive review of literature in 1980 and concluded that the postulated hazards of the continued use of antibiotic feeding could, at that time, neither be proven nor disproven. If evidence has accumulated since that time, it should be weighed on the same scale as the previous reports. This requires a rational approach and, frankly, we have not seen evidence of that. This is disturbing. The advocates of a ban are still vocal and, in their determination to accomplish something, have chosen to ignore the larger body of evidence in favor of a small number of reports and editorials in which an excessive amount of "editorial license" was exercised. For instance, at the same time the CDC report was being "summarized" by media persons throughout the country, and at the same time that certain members of Congress were proposing legislation as an over-reaction to the CDC report, a few scientists were studying the recent report in the October Journal of Clinical Microbiology by Atkinson and Lorian, who tested the resistance of nearly 6 million bacterial strains to commonly used antibiotics in hospitals. They concluded that bacterial susceptibility (to antibiotics) on a national scale has remained virtually unchanged during the last decade.

We are not suggesting that the paper by Atkinson and Lorian is the final answer. Nor should we pretend that the paper by Holmberg et. al is the final solution. The point is, over 6,000 scientific papers have been published on the subject of bacterial resistance since 1971 in the English language alone. Hopefuly, the answers to some of the pertinent questions can be derived from all this work. It would be irresponsible to move hastily - without a review of the science.

Further, with regard to public health, some consideration must be given to the trade-off which could occur between the therapeutic and subtherapeutic uses of antibiotics, especially penicillin and tetracyclines. It is not inconceivable that, should the incidence of clinical morbidity increase in the absence of subtherapeutic antibiotic use, more animals would require therapeutic treatment which may result in more total antibiotic use. This is an unknown. It is known, however, that therapeutic use of antibiotics also contributes to the reservoir of resistant bacteria. The therapeutic use in animals is small --- especially compared to such use in human medicine. Steele has estimated that the veterinary use of therapeutic doses of penicillin and tetracyclines is only 20% as great as such use in human medicine.

SUMMARY

In summary, so that there is no misunderstanding, the National Cattlemen's Association recognizes that there is an important scientific debate on the issue of antibiotic safety. We are here neither to defend or condemn the use of feed grade penicillin and tetracyclines in livestock and poultry production. Our objective is merely to stress the importance of basing every decision on the best scientific information available.

Mr. GORE. Thank you very much.

I had thought our next witness was Lee Boyd, with the American Feed Manufacturers Association, but you're taking his place, Mr. Klinger, is that right?

Mr. KLINGER. Yes, sir.

Mr. GORE. Your name is——

Mr. KLINGER. I'm Charles Klinger and Mr. Boyd, though, is accompanying me.

Mr. GORE. All right. And what is your position with the American Feed Manufacturers?

Mr. KLINGER. Actually, I represent a member company, Central Soya Co., Fort Wayne, IN.

Mr. GORE. Excuse me?

Mr. KLINGER. I'm actually from a member company, Central Soya Co., Fort Wayne, IN.

Mr. GORE. I see, and what is your—you're director of regulatory compliance with Central Soya Co.

Mr. KLINGER. Correct.

Mr. GORE. Is that right?

Mr. KLINGER. Correct.

Mr. GORE. All right, very good. Welcome. Please proceed.

Mr. KLINGER. Thank you. I do appear before you today on behalf of the American Feed Manufacturers Association, which is the national association representing manufacturers of over 70 percent of the primary formula of livestock and poultry feed sold annually in the United States. As I mentioned earlier, Mr. Lee Boyd, the AFMA vice president for feed control and nutrition is also present.

As background, my responsibilities at Central Soya include regulatory compliance matters for both feed and food products. I have been a member of AFMA's Feed Control Committee since 1959 and served as chairman for 13 years.

It was during that period that the antibiotic controversy came into being and continues to this day. Consequently, I am well acquainted with the subject in question, as is Mr. Boyd, who has had AFMA staff responsibility for regulatory compliance since 1960.

I think it is pertinent to address some previous questions concerning subtherapeutic and therapeutic uses of drugs. Actually, we characterize three different classes of levels of drugs. One is to increase the rate of growth and/or feed efficiency in conversion to animal products. This is characterized as subtherapeutic and low-level.

Second, also, apparently subtherapeutic in the eyes of FDA, there are elevated levels which are used to protect and promote animal health, that is, prevention of disease.

The third category, which is characterized as therapeutic, would be treatment of ill animals.

We must also recognize that we're talking about feed—or drugs that are administered through the feed and that these same drugs, penicillin and tetracycline, are available in other forms for administration at the local level, such as water medication, injectibles.

With regard to the true low-level use of antibiotics—and again, we could characterize these as maybe 5, 10, 15 grams per ton, just to give you a relationship, these have had important economic implications for consumers in lowering the cost of food.

However, the use of penicillin and the tetracyclines at these low levels is today very minimal. There are other drugs fulfilling this purpose.

In this second category, health protection, we could characterize these levels at perhaps 50 to 100 grams per ton, occasionally even 200 grams per ton could fit this category. It is by far the most important use of antibiotics with respect to economical production of high-quality food of animal origin. Health protection represents the major use of these antibiotics.

The third purpose, essentially the treatment of disease, is limited. We're talking about the extremely high levels for short-term duration and we must recognize that both economic and quality factors are adversely affected with any animal illness.

Antibiotics primarily for the subtherapeutic use, but sometimes therapeutic use, are normally supplied by our industry as an ingredient of animal feed. They may be incorporated into feeds by commercial feed mills as a service or even added to the feed at the farm or feeding level by the animal feeder.

Since antibiotics for these purposes must be received by the animal on a routine basis, feed is the natural means of administration. It is logical—a logical conduit and an economical approach to provide the antibiotics from the manufacturer through the distributor to the animals to be fed.

At this point, I would like to omit part of the prepared statement and add some oral comments. We'd like it to be recognized that the commercial feed manufacturers and mixers have little proprietary interest in the animal drugs themselves. Our products are essentially nutritional packages which may or may not contain medication for the animal. Our product, commercial animal feed, is simply, again, the logical and economic conduit to provide medication to the animal. Yet, we have an intense interest in safe, effective and economical animal drugs because our success is directly tied to the success of the animal producer.

The AFMA board of directors just recently approved a position paper on the use of animal drugs which was presented to FDA Commissioner Young. In this statement, our industry avows complete support for discontinuing use of any animal drug if it is found by legitimate and scientific findings to be unsafe.

Continuing efforts by the Food and Drug Administration to curtail the use of penicillin and the tetracyclines does concern us. It concerns us because we believe the scientific evidence to support such action is absent. For example, we have only to observe the effects of a similar restriction on the use of certain antibacterials in England. That is, a mirror image, if you will, of what FDA is attempting to achieve. It is our understanding, and of course, this was previously discussed, that after 13 years of such restriction, including the use of prescriptions, the status of human health has not been altered, nor has the use of these drugs been lessened.

Of primary concern is the potential change of emphasis from protection of animal health to one of treatment of disease. This country has enjoyed the benefits of safe, wholesome and economical supplies of milk, meat, and eggs perhaps more than any other country in the world. The major use of antibiotics has been for health protection.

In 1977, then Commissioner Kennedy, overruling the tetracycline recommendation from the National Advisory Food and Drug Committee, admitted the risk was theoretical. He stated that no specific instance in which human disease was more difficult to treat because of drug resistance arising from an animal source could be documented. This, in light of millions of tons of antibiotic-medicated feed being fed over a period of approximately 30 years. Has anything happened to change this position?

We do not intend to present ourself, the feed industry, as technical experts with respect to the antibiotics, but we can and do make logical assessments of available information. The CDC study, as published in the New England Journal of Medicine, is a case in point.

Mr. Boyd, of the AFMA staff, is a member of a party of six animal industry representatives, who met in Atlanta with two of the CDC report authors in a session lasting several hours. The impressions gained through that in-depth discussion are in sharp contrast with the editorializing of the report in the Journal and the general press.

At this point, Mr. Chairman, I'd like to ask Mr. Boyd to make a comment in that there seems to be some mis—some confusion as to the drug levels that were fed to the beef cattle, whether they be therapeutic or subtherapeutic.

Mr. Boyd. Mr. Chairman, can you hear me all right?

We had a very interesting discussion at CDC and it was most enlightening. I found Dr. Holmberg and Dr. Cohen very sincere individuals and I think they may honestly feel that they traced Salmonella to that farm. But when you read the report, I grant an epidemiologist must have an inquisitive mind, but I think when you read his report, you also need an inquisitive mind.

The first thing that struck me is that they said they were feeding approximately 100 grams of antibiotic daily to 105 animals. Now, that's approximately a gram per head per day. I asked them where they got the information. It was based on estimates, but I said, "You'd better go back and check your figures. As a matter of fact, we'd like to talk to those people, too, to find out just exactly what was fed," and they said the information was confidential—that is, the source was.

But in checking this out, a gram per head per day far exceeds any legal dose of tetracycline to be fed for an extended period of time. The normal level on routine feeding is about 70–75 milligrams per head per day. A gram per head per day is about 14-fold that level.

Now, whether the animals were receiving a subtherapeutic level or a therapeutic level, I don't know at this point in time, but I do know, making reference to some comments by Dr. Hays and others, that if they fed a therapeutic level for a long period of time, and if we assumed the cattle were the source of Salmonella—and I'm not sure that's the case—then that antibiotic pressure on that environment in those cattle was tremendous compared to low-level feeding of antibiotics. That's just one of the questions that occurred to us and we never really got an answer.

Mr. Klinger. Quickly, just to conclude, the so-called antibiotic question, the development of resistance and its implications is, in

our opinion, an unresolved scientific issue. Unfortunately, there's been more emotion than fact. We believe it will be best determined as a scientific issue by evidentiary type hearings, and, of course, we now understand that FDA plans to hold just such a hearing, and hopefully the facts developed at that time will permit a logical and rational decision on what action, if any, should be taken.

Thank you for this opportunity to appear.

[The prepared statement of Mr. Klinger follows:]

STATEMENT OF

THE AMERICAN FEED MANUFACTURERS ASSOCIATION

before

THE SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT
HOUSE COMMITTEE ON SCIENCE & TECHNOLOGY

ON ISSUES RELATED TO

DEVELOPMENT OF RESISTANCE OF ANTIMICROBIAL DRUGS

December 18, 1984

Charles W. Klinger
Director of Regulatory Compliance
Central Soya Company, Inc.
Fort Wayne, Indiana

AMERICAN FEED MANUFACTURERS ASSOCIATION, INC. • 1701 N. FT. MYER DRIVE • ARLINGTON, VA. 22209 • TELE: 703/524-0810

Mr. Chairman, I am Charles W. Klinger, Director of Regulatory Compliance for Central Soya Company of Fort Wayne, Indiana. I appear before you today on behalf of the American Feed Manufacturers Association, the national association representing manufacturers of over 70% of the primary formula livestock and poultry feed sold annually in the U.S. Accompanying me today is Mr. Lee Boyd, AFMA Vice President for Feed Control and Nutrition.

As background, my responsibilities at Central Soya include regulatory compliance matters for both feed and food products. I have been a member of AFMA's Feed Control Committee since 1959, and served as Chairman for thirteen years. It was during that period that the antibiotic controversy came into being and continues to this day. Consequently, I am well acquainted with the subject in question - as is Mr. Boyd who has had AFMA staff responsibility for regulatory compliance since 1960.

My comments will be brief. They will touch on the following points:

(1) The purpose of antibiotics in animal feeding.

(2) The role of feeds.

(3) The regulatory environment associated with that role - i.e., the part played by the drug industry, federal and state authorities, the feed industry, and the feeder.

(4) The AFMA policy position on animal drugs - including antibiotics.

(5) The AFMA view of the current situation - including the Center for Disease Control (CDC) report and numerous press stories on same.

To begin with, antibiotics are used in animal production for three purposes:

(a) To increase rate of growth and/or efficiency of feed conversion to animal products,
(b) To protect and promote animal health, and
(c) For treatment of ill animals.

The first purpose, associated with true low level use of antibiotics, has important economic implications for consumers in lowering the cost of food. Antibiotics have been used at low levels in animal feeding for over 30 years without scientifically proven health risk. This has contributed to consumer savings totalling billions of dollars.

The second use, health protection, involves higher subtherapeutic levels. It is, by far, the most important use of antibiotics with respect to economical production of high quality food of animal origin. Health protection represents the major use of antibiotics.

The third purpose has limited use since the goal, from an economic and quality viewpoint, is an ongoing healthy animal. Both economic and quality factors are adversely affected with any animal illness.

Antibiotics for the first and second purposes are normally supplied as an ingredient of animal feed. They may be incorporated into feeds by commercial feed mills or added to the feed at the farm or feeding level by the animal feeder. Since antibiotics for these purposes must be received by the animal on a routine basis, feed is the natural

means of administration. Consequently, commercial feed is a logical conduit or bridge between the antibiotic manufacturer/distributor and the animal to be fed.

Antibiotics are developed through research by drug firms, who must pursue extensive testing to prove their suitability for use in animal production.

All animal drugs, including the various antibiotics, are regulated by the federal Food & Drug Administration (FDA) and by state feed control services. FDA must, by law, determine such products have been proven safe and effective by their sponsor prior to publishing regulations governing their distribution and use. As third parties, feed manufacturers depend on the FDA safety determination which is beyond the usual and ordinary capability of the vast majority of feed manufacturers.

The federal (FDA) regulations governing antibiotic use are specific as to animal, purpose, level, and conditions of use. Commercial mills are routinely inspected by federal and state authorities to monitor incorporation into feeds in conformance with these regulations and good manufacturing practices, and to insure the proper labeling of the antibiotic containing feeds. The animal feeder, for his part, is expected to use antibiotics and antibiotic containing feeds in conformance with label directions.

We use antibiotics only after they are deemed safe by FDA. We incorporate them into our feeds in compliance with the needs and expressed desires of our customers. We do so as a service.

AFMA's interest - and, indeed, animal agriculture's interest - in antibiotics, as with any animal drug, must be in the product's ability to make a positive contribution to the economical production of wholesome food of animal origin. If a product impinges on the wholesomeness of food or otherwise adversely affects it, we will support action that its use be dropped. This is explicit in our attached policy statement. However, the determination of a product's effect and its future should be based on scientific fact and not emotion. Facts, as contrasted to emotion, have been in short supply on the antibiotic issue. It was an absence of factual information that led Congress several years ago to instruct FDA not to proceed against antibiotics on an admittedly theoretical basis but to assemble additional information.

While we do not intend to present ourselves - i.e., the feed industry - as technical experts with respect to antibiotics, we can and do make logical assessments of available information. The CDC study, as published in the NEW ENGLAND JOURNAL OF MEDICINE, is a case in point. Mr. Boyd of the AFMA staff, as a member of a party of six animal industry representatives, met in Atlanta with two of the CDC report authors in a session lasting several hours. The impressions gained through that in-depth discussion are in sharp contrast with the editorializing of the report in the JOURNAL and the general press. Based on that discussion, the report is not the alleged "smoking gun" or "missing link". Mr. Boyd will be pleased to elaborate on those impressions if you so desire.

The so-called antibiotic question - the development of resistance and its implications, is an unresolved scientific issue. Unfortunately, there has been more heat than light shed on it. It will be best decided, as a scientific issue, by an evidentiary type hearing. We understand FDA plans to hold just such a hearing. Hopefully, the facts developed at that time will permit a logical and rational decision on what action, if any, should be taken.

We thank you for this opportunity to present our comments. We will be pleased to provide any desired additional information and to entertain any questions they may have generated.

Mr. GORE. Thank you very much.

Our next witness is Dr. Richard Gustafson, associate research fellow with American Cyanamid Co.

Doctor, welcome and please proceed.

[The biographical sketch of Dr. Gustafson follows:]

Richard H. Gustafson
28 Wood Hollow Road
Lawrenceville,
New Jersey 08648
(609) 799-2762

Academic

1951	B.S.	University of Rhode Island (Zoology)
1958	Sc.M.	Brown University (Bacteriology)
1961	Ph.D.	Rutgers, Institute of Microbiology (Virology)

Employment

1951-53 - Fort Detrick, MD (Military)
Chemical Corps BW Program - Bacteriologist

1953-54 - Pine Bluff, AR (Military)
Chemical Corps BW Program - Bacteriologist

1954-57 - Eaton Laboratories, Norwich Pharmacol Co., Norwich, NY
Parasitologist

1961-74 - Carter Wallace, Cranbury, NJ
Manager, Virus Research Group

1974-Present - American Cyanamid Co., Agricultural Research Div., Princeton, NJ
1974-78 - Group Leader, Microbiology Discovery
1978-82 - Manager, Antibiotic Products
1982-Present - Associate Research Fellow

Publications

M. P. Natt, R. H. Gustafson, J. O'Connor, 1957. Comparison of Antoxyurid Activity of NF-23 (Ethyl 3-(5-Nitro-2-Furyl)-Acrylate) and Piperazine Citrate Against the Mouse Pinworm. Syphacia obvelata, Am. J. Trop. Med. Hyg., 6:389.

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Additional Presentations

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Incidence and Antibiotic Resistance of Salmonella in Market Swine, Washington, D.C., January 30, 1976. Meeting of Antibiotics in Animal Feeds Subcommittee of the National Advisory Food and Drug Committee.

Nonmedical Uses of Antibiotics and Public Health. Invited Speaker, School of Public Health, Harvard University, 1974, 1975, 1976, 1977, 1978, 1979, 1981, 1982, 1983, 1984.

Avoparcin and Salmonella: A Review. Berlin, May 10, 1979. Fachgesprach uber Wachstumforder; Institut fur Veterinarmedizin des Bundesgesundheitsamt.

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Chairman, Antibacterial Research Criteria Task Force, Animal Health Institute.

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Dr. GUSTAFSON. Thank you, Mr. Chairman, members of the committee.

I am Dr. Richard Gustafson, research fellow in the agricultural research division of the American Cyanamid Co. For 10 years, I have been involved in research on animal feed antibiotics and the mechanism and significance of bacterial resistance.

In 1949, Cyanamid scientists discovered the usefulness of low levels of antibiotics in animal feed to promote faster growth and produce more meat per pound of feed consumed. The company manufactures and markets chortetracycline and other products and is the largest supplier of feed additives for animal nutrition and health.

I appreciate this opportunity to express briefly our views to the committee on the subject of resistance to antimicrobial drugs. I will submit a more detailed statement for the record.

Animal feed antibiotics at subtherapeutic levels have helped to provide the American people with the most readily available supply of safe, wholesome and economical meat and poultry products any country has ever known.

Over 34 years of use with hundreds of millions of animals and hundreds of billions of pounds of meat consumed, there have been no demonstrated incidence of human disease related to animal feed antibiotics. Cyanamid believes that there is no justification for additional restrictions on the tetracyclines and penicillin for subtherapeutic use in animal feed.

Feed antibiotics, bacteria resistance, and antibiotic effectiveness in humans have been studied extensively for more than 20 years. Several Government-sponsored and independent panels of experts in this and other countries have reviewed the available data and no evidence has emerged that low-level feed antibiotics have any adverse effect on human health.

Unfortunately, that's not what the American public has been led to believe. In recent months, the public has read and heard statements about—and I quote: "The frightening side effects we could suffer from the meat we eat." They've been asked to—and I quote: "find out if there's much more in meat that could kill you." The implications are terrifying and they are totally unwarranted and unsubstantiated.

I'd like to dispel some of the myths and misconceptions today and clarify the meaning and significance of recent reports on animal feed antibiotics and human health. First, resistance to animal antimicrobial drugs is not increasing at an alarming pace. In most cases, it seems not to be increasing at all. Barbara Atkinson and Dr. Victor Lorian of the Bronx Lebanon Hospital in New York City analyzed data on almost 6 million bacterial strains tested in 272 hospitals over a 12-year period. More than 43 million separate sensitivity tests were done with 16 common antibiotics.

They reported that bacterial susceptibility on a national scale has remained virtually unchanged during the last decade. Resistance to tetracycline, the drug most commonly used in animal and poultry feed, decreased in four of the six bacterial species analyzed. Antibiotic resistance problems do occur in human clinical medicine, but they are undoubtedly a consequence of antibiotic use in

human medicine, and in most cases, alternative and effective antibiotics are available.

Second, the public has been led to believe that the recent report on 18 cases of salmonellosis in the Midwest provides credence that resistant bacteria were linked to feed antibiotics. That is not true. Independent scientists have been critical of that report. Its conclusions about feed antibiotics is based on assumptions, rather than evidence.

The resistant Salmonella were not isolated from the meat, from the beef herd, the beef farm, or any point in the distribution chain. The authors assumed that Salmonella moved from a sick dairy calf to the beef herd and through all the processing steps, even though they were not found in any of them.

Further, 70,000 pounds of beef, which, according to the report, could have included meat from both the suspect herd and other herds, were distributed. That's enough meat for 280,000 Quarter Pounders, but only 13 people who ate them got sick. No other food poisoning was reported. Why?

No link has been proven between resistant Salmonella from the sick people and the beef herd and certainly no link between subtherapeutic chlortetracycline and human disease.

In the mid-1970's, scientists, using protocols approved by the FDA, demonstrated and published studies that showed that subtherapeutic tetracyclines fed to calves did not contribute, either to the selection or persistence of resistant Salmonella.

Now, let me direct your attention back a few years. In 1980, after an intensive review of the literature, the National Academy of Sciences, under contract from the FDA, stated that, and I quote: "There are no data linking human illness with the subtherapeutic use of antimicrobials in any aspect of animal husbandry."

The Academy report concluded that the hazards to human health were neither proven nor disproven. The report recommended specific research in four areas to help resolve the question of subtherapeutic feed additives and antibiotic resistance, and again, I quote: "To provide a useful scientific background for policymakers." That research has not been conducted. The principal study funded by the FDA in response to that recommendation is the so-called Seattle-King County study. It's an excellent work, but it does not address subtherapeutic feed additives. It primarily deals with enteric disease and the epidemiology of Campylobacter.

The authors do state that further specific study is necessary to determine any relationship that may exist between poultry feeding practices and antibiotic resistance in this organism. Many of the data and statements in the report, however, are consistent with and support Cyanamid's position on these concerns.

For example, the authors state that the presence of tetracycline resistance plasmids and Campylobacter, and I quote: "may have little practical clinical significance." They note that most tetracycline-resistant strains of Campylobacter could transfer their resistance only to other Campylobacter species. R-factors could not be introduced or transferred into E. coli and probably other indigenous flora in the gut of the animals. The authors stated that the similarities between resistant bacteria isolated from retail poultry and from food poisoning patients could easily support a hypothesis that

the chickens were infected by humans, or both derived their isolates from another source, and these are the authors' words, not mine.

In short, this study, the principal work funded by the FDA on the question of antibiotic resistance, did not address animal feed antibiotics, but it found nothing to implicate them with any adverse human health effects.

Three studies recommended in 1980 by the National Academy of Sciences are currently in progress. They're being sponsored by several member companies of the Animal Health Institute, an industry organization. We believe that these studies will have greater relevance to this issue than the Seattle-King County report.

The final point I would like to make concerns the alternatives for tetracyclines. A common misconception is that equally effective antibiotics not used in human medicine are available for use in animal feeds. That's not true. Twenty-one antibacterials have been approved by the FDA for animal feed use. Most do not prevent respiratory or other systemic diseases. Some are effective only for growth promotion and feed efficiency.

By contrast, FDA has approved 30 disease-prevention and control claims for chlortetracycline in all major food-producing animal species, and none of the so-called alternatives equals the broad spectrum, effectiveness, safety, economy, and general usefulness of the tetracyclines.

The control—I'm sorry, the Council on Agricultural Science and Technology has stated that—and I quote: "The tetracyclines and penicillin have been and remain front runners * * *. Totally viable alternatives do not exist."

To summarize, Mr. Chairman, the American people have been badly misled about antibiotic resistance and the safety of their animal food supply. Bacterial resistance in animals and the relationship to human health has been studied intensively since the 1960's and subtherapeutic animal feed antibiotics have not been linked to human illness.

Today, the preponderance of credible evidence and 34 years of practical experience provides no indication that animal feed antibiotics represent a hazard to human health. The benefits of subtherapeutic tetracyclines and penicillin are widespread and well documented in reducing disease in livestock and poultry and the result is economic savings.

I'm confident that these facts will be fully brought out and the issue resolved according to the procedures established by law at an administrative hearing which the FDA, I believe, has already agreed to hold. Thank you.

[The prepared statement of Dr. Gustafson follows:]

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Agricultural Division
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STATEMENT

of

AMERICAN CYANAMID COMPANY

on

RESISTANCE TO ANTIMICROBIAL DRUGS

before the

INVESTIGATIONS AND OVERSIGHT SUBCOMMITTEE

of the

U.S. HOUSE OF REPRESENTATIVES COMMITTEE

on

SCIENCE AND TECHNOLOGY

December 18, 1984

SUMMARY

In 34 years of widespread use with literally hundreds of millions of animals, there have been no outbreaks of untreatable human or animal disease related to subtherapeutic use of tetracyclines in animal or poultry feed. Over that time, the social and economic benefits of these products have been amply demonstrated.

From the 1960s to 1980, a number of thorough scientific reviews by respected organizations in this country and abroad failed to relate animal feed antibiotics to human disease. The National Academy of Sciences stated in 1980 that "there are no data linking human illness with the subtherapeutic use of anti-microbials in any aspect of animal husbandry," but the existence of a public health hazard has been "neither proven nor disproven." It recommended further specific research to the FDA to provide an adequate scientific base in order to permit a responsible decision. FDA has not conducted those studies, but because of their importance, they are now being investigated under sponsorship of the Animal Health Institute, an industry organization.

Since September 1984, several reports of other studies relevant to the issue have been published.

The conclusions of the so-called Holmberg-CDC report, which claims to link subtherapeutic antibiotics in animal feed to 18 cases of salmonellosis, are not supported by the evidence presented. However, this investigation by CDC has resulted in much sensational but unwarranted publicity that is undermining public confidence in its animal food supply.

The Lorian study of bacterial susceptibility and resistance patterns in 242 hospitals over 12 years concludes that resistance to 16 commonly used antibiotics remained virtually unchanged from 1971 to 1982. Tetracycline-resistance actually decreased in four of six bacterial species studied.

The Seattle-King County study, funded by FDA and conducted among 320,000 subjects over 20 months, found no link between feed antibiotics and human illness, although it did not address that issue directly. Data and statements contained in the report, however, support Cyanamid's position on this issue.

Cyanamid believes that FDA is no closer to scientific justification for additional restrictions on tetracyclines and penicillin in animal feed today than it was in the past. The proper course of action is for FDA to proceed to adjudicatory hearing, the forum provided by law, to determine all

the facts and resolve the issue according to established procedure.

When all the facts are known, the American people will recognize that subtherapeutic animal feed antibiotics represent no threat to human health, and they will be reassured that their supply of meat and poultry products is indeed safe as well as nutritious, appetizing and affordable.

INTRODUCTION

My name is Dr. Richard Gustafson. I am a Research Fellow in the Agricultural Research Division of American Cyanamid Company. For 10 years I have been involved with research on animal feed antibiotics, the mechanisms and effects of bacterial resistance to antibiotics and the significance of that resistance to humans and animals.

In 1949, Cyanamid discovered the effectiveness of subtherapeutic use of tetracycline in animals and poultry to prevent disease, promote faster growth and increase feed efficiency. It introduced Aureomycin chlortetracycline for those purposes in 1950, and has been continuously involved in research and development of antibiotic feed additives and other products to aid animal nutrition and health. The company today is the leading supplier of antibiotic feed additives to the U.S. livestock and poultry industries.

Cyanamid commends the Subcommittee on Investigations and Oversight for undertaking this hearing to determine the current status and latest scientific facts of the antibiotic-resistance problem as it pertains to antibiotics used in animal feed.

In recent months, the public has been subjected to much inaccurate but highly sensational coverage in the popular press which has produced unwarranted fear of animal food products. In newspapers and on network television, the public has seen and heard statements about "the frightening side effects we could suffer from the meat we eat." They have been asked to "find out if there's much more in meat -- besides fat and cholesterol -- that could kill you." And they have been told that "We are looking at hundreds of thousands of antibiotic-resistant bacterial infections."

The implications are alarming, and without foundation.

The American people are being given badly unbalanced and misleading information about the safety of their animal food supply.

American livestock are the healthiest in the world. The American people have the most readily available supply of safe, wholesome, appetizing and economical meat and poultry products any country has ever known. Experts agree that subtherapeutic feed antibiotics have contributed greatly to those facts. And the preponderance of credible evidence from recent studies, as well as from 34 years of practical experience, shows that animal feed antibiotics do not represent a hazard to human health.

Cyanamid, therefore, welcomes this opportunity to help dispel the myths and misconceptions reported in the media on animal feed antibiotics and human health, and to help clarify the scientific meaning and significance of recent studies and reports.

BACKGROUND

Antibiotics at subtherapeutic levels have been widely used in animal and poultry feeds for 34 years to prevent and control disease, promote faster growth and produce more meat per pound of feed consumed. This practice has significantly improved both the quality and reliability of our animal product food supply by reducing the incidence and severity of bacterial disease. It also allowed development of our current, highly efficient food animal production system where energy, space, capital and manpower requirements have been reduced to a cost-efficient minimum.

Consumers share in these benefits. Americans spend a lower percentage of their income than do residents of any other country for safer, more nutritious and appetizing meat and poultry products.

However, questions concerning the use of animal feed antibiotics and antibiotic-resistance persist. The subject is highly complex. Resistant bacteria are selected by therapeutic use of antibiotics in human and veterinary medicine, and from subtherapeutic use in animals. Isolating the effects of use in each of these areas is extremely difficult, and the results are not likely to be clear-cut. Furthermore, resistant bacteria may be harmless, and they may or may not be capable of transferring their resistance to disease-producing organisms.

The matter has been studied by governmental, academic and industrial scientists. Respected experts have been unable to reach a consensus on the existence of any public health hazard from feed antibiotics.

Numerous organizations have conducted extensive scientific

reviews to consider the possibility of hazard to human health from the use of antibiotics in livestock:

In 1960 the Netherthorpe Committee was established in the United Kingdom. A subcommittee concluded that there was no evidence of hazard, although at the time of their deliberations transmissible antibiotic resistance was not generally known.

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In 1968 the Swann Committee in the the U.K. did not report any hazard to man or animals from use of antibiotics in poultry or swine. Because of an outbreak of salmonellosis in humans linked to therapeutic use of antibiotics in sick calves, however, the committee recommended that tetracyclines be permitted only on veterinary prescription. The restrictions were put into effect in 1971.

Recently it has been acknowledged that no reduction in antibiotic resistance in humans has resulted, and no change in human health experience has been observed. Salmonella isolated from cattle were 40% resistant in 1965 and 70% resistant in 1978. In September 1982, Lord Swann called for a "new committee of inquiry to have a fresh look, in the light of present knowledge, at the best use of antibiotics." He said his committee only got it "very partly right" and that enthusiasm for the recommendations on antibiotic controls overshadowed the major recommendation for improved husbandry and management.

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In 1970 a symposium on drug-resistant pathogenic bacteria was organized by the New York Academy of Sciences. Speakers were unable to link antibiotics in animal feeds to health problems in man, but suggested that more research was needed.

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In 1972 FDA's Task Force on the Use of Antibiotics in Feed reported that because the feeding of some antibiotics increases the prevalence of resistant bacteria in animals, these resistant bacteria may be a significant source of resistant bacteria for man; therefore, there may be a human health hazard. Seven of the fifteen Task Force members filed a minority report disagreeing with major conclusions.

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In 1976 a subcommittee of FDA's National Advisory Food and

Drug Committee recommended that the use of penicillin be prohibited and tetracycline be continued for disease prevention only where effective substitutes are not available. The parent committee rejected the subcommittee's recommendation with regard to tetracyclines, saying that restrictions were not justified.

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In 1979 the Office of Technology Assessment issued a report which pointed out: "This risk from resistant plasmids of animal origin is not quantifiable....The majority of resistance in human bacterial populations is probably caused by widespread use of antibacterials in humans...but the enormous pool of R-plasmids that now exists in animals... must be regarded as a threat to the therapeutic value of antibacterials in both human and animal disease."

* * * * *

In 1980 under contract to FDA, the National Academy of Sciences (NAS) performed an extensive review and concluded "the hazards to human health have been neither proven nor disproven...." The committee said that "there are no data linking human illness with the subtherapeutic use of antimicrobials in any aspect of animal husbandry," but that it is still possible that hazards may exist; therefore, adequate research is needed to explore this area. They further stated that it was critically important to define separately the resistance effects of therapeutic and subtherapeutic antibiotic uses in animals.

The NAS report said that an ideal study would be able to relate, without conjecture or speculation, antimicrobials in feed to changes in disease caused by resistance in humans who have been "exposed to animals or meat products during processing, handling or especially consumption."

NAS recommended specific research in four areas: the relationship between the appearance of resistant bacteria and the dosage of tetracycline antibiotics fed or otherwise administered to beef cattle, pigs and chickens; a comparison of vegetarians and meat-eaters to measure tetracycline-resistant bacteria voided from the intestine; a study of workers in slaughterhouses, their families and neighborhood controls to determine any tendency for resistant bacteria from this source to become established in humans by colonization; and a study of urinary tract infections in women who work in the meat processing industry.

These studies, NAS said, "would provide a useful scientific background for policymakers."

They have not been conducted by FDA. Because of their critical importance, however, three studies addressing two areas recommended by NAS are now in progress under sponsorship of the Animal Health Institute, an industry organization. Results are expected late in 1985.

RECENT EVENTS

In September 1984, Dr. Scott Holmberg of the Centers for Disease Control (CDC) published in the New England Journal of Medicine a report on 18 cases of salmonellosis in the midwest, claiming to link them with the use of feed antibiotics. This report led to the surge of inaccurate and frightening publicity cited earlier, and has fostered a growing but unfounded distrust by the American public of its meat supply.

Cyanamid contends that the conclusion relating to subtherapeutic feed antibiotics in this report is based on unproven assumptions rather than documented fact. Two alternate, independent explanations of probably greater importance were virtually ignored by the authors. The conclusion is not established by the evidence presented; the study fails to provide the 'missing link,' as claimed, between an outbreak of diarrhea on a dairy farm and the appearance of the unusual organism in patients hundreds of miles away.

The resistant salmonella which caused food poisoning in 18 people, and allegedly came from hamburger from one beef herd which had been fed chlortetracycline, was never isolated from the meat, from any processing step, from the beef herd, or the beef farm. The authors only assumed that resistant salmonella moved from a sick dairy calf to a neighboring beef herd and up the food chain because bacteria isolated from the sick people and the dairy calf were similar.

The simplest and most probable explanation is that an infected dairy cow -- where the resistant salmonella were known to exist -- was sold for meat. Some 70,000 pounds of beef, which the report says "could have included meat from both the suspect herd and other herds," were distributed. No other food poisoning was reported; however it appears that CDC did not investigate other Salmonella newport cases where sensitive salmonella were present.

In contradiction of the Holmberg-CDC report's assumptions, two industrial scientists, Drs. Layton and Girard, have demonstrated in controlled scientific studies that subtherapeutic tetracyclines fed to calves did not contribute either to the selection or persistence of resistant-salmonella.

These studies were carried out at the direction of FDA, using protocols approved by the agency before the studies were initiated. Their work was published in Antimicrobial Agents and Chemotherapy (Girard, 1976) and Zentralblat fur Veterinar Medicin B (Layton, 1975).

Opponents of feed antibiotics made much of the fact that one person infected with the resistant salmonella actually died. The media emphasized the distorted implication that the bacteria responsible for the death were acquired from eating the suspect meat. That is incorrect. The patient was already in the hospital for a serious abdominal injury that required surgery. He acquired the salmonella infection after sigmoidoscopy when the hospital staff used the same equipment that had been used immediately prior on a salmonellosis patient. The patient who died had not eaten meat from the beef herd singled out in the report.

The escalation of claims based on the Holmberg-CDC study should also be noted. The report itself claims, erroneously, only that "antimicrobial-resistant bacteria of animal origin can cause serious human disease...." (Emphasis added.) An editorial accompanying publication of the report claims that bacteria from calves fed subtherapeutic doses of antibiotics "caused illness in 18 people...." (Emphasis added.) And finally, in the popular press, the public read and heard talk about 'hundreds of thousands of antibiotic-resistant bacterial infections,' and, in effect, that 'the meat you eat can kill you.'

These alarming statements to the American public are all based on the inadequate facts, undemonstrated assumptions and unsupported conclusion relating to feed antibiotics in the Holmberg-CDC report.

* * * * *

In October 1984 Dr. Victor Lorian, director of the Division of Microbiology and Epidemiology at Bronx-Lebanon Hospital in New York City, published in the Journal of Clinical Microbiology a 12-year study of antimicrobial agent susceptibility and resistance patterns of bacteria in hospitals.

He concluded that "Bacterial susceptibility on a national scale has remained virtually unchanged during the last decade." The widespread belief that bacterial resistance to antibiotics is increasing at an alarming pace "is a myth."

His conclusion was based on analysis of 5,828,243 bacterial strains isolated from patients in 242 hospitals nationwide from 1971 to 1982 inclusive. The strains analyzed were those most frequently isolated, or those that produce

serious illness and significant mortality. Over 43 million separate senstitivity tests were performed with 16 commonly used antibiotics. Tetracycline-resistance actually decreased in four of six species analyzed.

He attributes the widespread perception that bacterial resistance to antibiotics is increasing to the fact that 6,383 papers on the subject have been published in the English language alone since 1971. Many are based on surveys conducted in a single institution. Some reports are supported by "very limited evidence," and some deal with even a single resistant strain.

Although local outbreaks of bacterial resistance do arise, they do not establish a trend. That "resistance may be a consequence of unbalanced antibiotic usage or due to a high rate of nosocomial infections," the report stated. Dr. Lorian at a later conference estimated that perhaps 20 hospitals out of 6,000 have such problems, and they are reversible. Those resistance problems "don't come from cattle," he said, or everybody who eats meat would show increasing resistance, at least to tetracycline. And tetracycline-resistance is decreasing.

* * * * *

In November 1984 the FDA released a study (Surveillance of the Flow of Salmonella and Campylobacter in a Community) conducted by the Seattle-King County Department of Public Health.

This study was funded by FDA as the principal study in response to the NAS recommendations in 1980 for additional research. It did not address the question of animal feed antibiotics in relation to human health.

Conducted over 20 months among 320,000 members of a health maintenance organization, the report concludes only that "further specific study should be undertaken to unravel any relationship that may exist between (geographical) poultry feeding practices...and susceptibility patterns," and that "further work must also be done to determine the relationship between carriage of a tetracycline R-factor...and tetracycline supplementation of poultry feed; the present study did not address this issue directly."

Many of the data and statements in the report are consistent with and support Cyanamid's position on these concerns.

The authors point out that the clinical significance of tetracycline-resistance in C. jejuni has yet to be determined. "Most patients with C. jejuni infection do not

receive antibiotic therapy, and tetracycline is not the drug of choice should an antibiotic be needed." The presence of these resistance plasmids is "of academic interest but may have little practical clinical significance."

Further, most of the tetracycline-resistant strains of Campylobacter bacteria could conjugally transfer their tetracycline-resistance only to other Campylobacter species. C. jejuni R-factors could not be introduced into E. coli. In other words, they could not transfer their resistance capabilities to other bacteria in humans.

Other study data note that tetracycline-resistance in campylobacter isolated from poultry processing plants was significantly less that that found in sick people or retail poultry outlets. There was no tetracycline-resistance found among salmonella isolated from processor poultry; the corresponding figure from retail poultry was over 30 percent. This suggests that bacteria which actually caused human illness were introduced during physical handling of poultry products.

Supporting that view, the report states that isolation rates for campylobacter in retail markets "were lowest on Mondays when display shelves were cleanest and products had been freshly received. On the other hand, handling of poultry at the retail level appeared to increase the likelihood of culturing C. jejuni."

The report also notes that humans were just as likely to acquire tetracycline-sensitive as tetracycline-resistant C. jejuni infections from poultry. And "a greater proportion of tetracycline-resistant as opposed to sensitive infections were attributable to drinking raw milk," yet tetracycline is seldom added to dairy animal feed.

And finally, the authors say that, taken alone, the similarities between resistant bacteria isolated from retail poultry and from food poisoning patients could "as easily support a hypothesis that chickens were infected by humans, or perhaps more reasonably, that chickens and humans derived their C. jejuni isolates from another large environmental reservoir."

* * * * *

In November 1984, based largely on the Holmberg-CDC report, the Natural Resources Defense Council, Inc. (NRDC) petitioned the Secretary of Health and Human Resources to withdraw approval for the tetracyclines and penicillin for use in animal feeds under the 'imminent hazard' provision of the Food, Drug and Cosmetic Act. A hearing has been scheduled

for January 10, 1985.

The petition relies heavily on projections based on data from the Holmberg-CDC study which, as has been shown, is of extremely limited scope, has been the subject of serious scientific criticism for failing to support its conclusion about feed antibiotics and is in a number of respects contradictory to the Girard, Layton, Lorian and Seattle-King County studies. The petition makes no mention of these other studies, even though they had been published or otherwise released to the public when the petition was submitted.

In its cover letter with the petition to Secretary Heckler, NRDC refers to a letter sent to her and President Reagan in 1983, signed by 300 scientists who supported the requested ban. No action was taken, but that letter also received a great deal of publicity at the time.

Dr. Lorian was asked to sign that letter and refused. "I don't believe that bacterial resistance from cattle can be spread to people in any dangerous way...."

THE QUESTION OF SUBSTITUTES

A common misconception, often stated, is that equally effective antibiotics not used in human medicine are available for substitution in animal feeds. It is not true.

Although 21 antibacterials have been approved by FDA for use in animal feeds, a report by the Council for Agricultural Science and Technology stated, "The tetracyclines and penicillin have been, and remain, front runners....Totally viable alternatives do not exist."

Most alternative antibiotics, unlike tetracycline, are not absorbed into the animal's bloodstream and therefore cannot be effective in preventing respiratory or systemic diseases. Some have no ability to prevent disease, but are effective only for growth promotion and feed efficiency.

None of the so-called alternatives equals the broad spectrum of effectiveness, safety and general usefulness of the tetracyclines. FDA has approved 30 disease prevention and control claims for chlortetracycline in all major food-producing animal species.

Antibiotics are not all alike, nor are the animals to which they are administered. The particular compound added to feed at any given time is based on the needs of the herd or flock. Thus chlortetracycline may be used for cattle in

areas where anaplasmosis is endemic, or in cattle recently shipped to a feedlot where the likelihood of respiratory disease is high.

Several suggested substitutes may also select for resistance to antibiotics used in human medicine. Since this is the basis for proposed restrictions on penicillin and tetracyclines, the use of substitutes which also select for resistance would present the same theoretical health hazards

CYANAMID'S POSITION

Cyanamid believes that there is no justification for additional restrictions on the tetracyclines and penicillin for subtherapeutic use in animal feed.

The subject of antibiotic feed additives, bacterial resistance,and human health has been studied intensively since the 1960s without conclusive result. Practical experience over 34 years, and the preponderance of credible evidence from recent studies, demonstrate both that tetracyclines and penicillin in animal feed have no cause-effect relationship to human disease and little if any to bacterial resistance in humans.

Yet the benefits of subtherapeutic tetracyclines and penicillin to the public are widespread and well documented. Feed antibiotics, of which tetracyclines and penicillin are the most widely used, have been estimated to save consumers $3.5 billion a year in the cost of meat and poultry products. Equally important is the reduction of clinical disease in livestock and poultry, helping to assure a safe, wholesome supply of meat, milk and eggs.

By reducing risk of disease, feed antibiotics make it feasible to assemble large numbers of animals and poultry at one location for more efficient management and best use of land, capital and labor.

In 1977, for example, fewer than half as many workers produced more than twice as much meat as in 1950, before the advent of feed additives.

- o 1950: 150 million Americans consumed 156 pounds of meat and poultry products per capita.
- o 1977: the real cost of meat and poultry had declined to the point that 216 million Americans consumed nearly 223 pounds per capita.
- o 1950-1977: the number of workers on all farms (including

family members and hired workers) declined more than 58%.

Science is no closer to finding problems with tetracyclines and penicillin in animal feed today than it was in 1977. An additional seven years have passed with no sign of the predicted 'epidemic of untreatable human disease.' And antibiotics continue to be effective in both humans and animals for their intended and FDA-approved uses.

Reason and good science must overcome sensational emotionalism on this issue of animal feed antibiotics.

Cyanamid believes that the proper course of action is for FDA to proceed to adjudicatory hearing, the forum provided by law, to determine all the facts and resolve the issue according to established procedures. FDA has already agreed to hold such a hearing. There is no need at this time for Congressional action.

Cyanamid is confident that, when all the facts surrounding this complex scientific issue are known, the American public will realize that subtherapeutic tetracyclines and penicillin in animal feed represent no threat to human health. And the public will be reassured that its supply of meat and poultry products is indeed safe as well as nutritious and affordable.

# # # # #

Mr. GORE. Thank you very much. Appreciate that and our final witness today is Mike Wehler, chairman of the antibiotic task force for the National Pork Producers Council. Mr. Wehler, welcome, and please proceed.

Mr. WEHLER. Thank you, Mr. Chairman.

In the interest of saving time, I will summarize my remarks for you, and also because my stomach tells me that I should have eaten an extra piece of ham for breakfast this morning. [Laughter.]

I wasn't prepared to sit through the entire session. On the farm, we normally take a break for lunch, but we certainly——

Mr. GORE. Well, we were going to do that, but we—it looked like we could get through so please accept our thanks for the patience of all the witnesses here today——

Mr. WEHLER. Well, I understand——

Mr. GORE [continuing]. For taking so long.

Mr. WEHLER [continuing]. And appreciate that, Mr. Chairman.

My name is Mike Wehler; I am a pork producer from Plain, WI, a small community, about 600 people. I represent the Wisconsin pork producers on the board of directors of the National Pork Producers Council. As the statement indicates, we do have 38 affiliate State associations and represent over 110,000 identified pork producers throughout the Nation.

Pork producers are at least as concerned about any—are at least as concerned as any other segment of the population about the health and well-being of—of our fellow citizens. When there is a problem involving hog production methods, the Nation's pork producers, through their organization, the National Pork Producers Council, work closely with Government agencies and others to correct that problem.

The NPPC executive committee recently established a producer task force to study the use of antibiotics in pork production. I'm happy to—to announce to you that many of the members of our task force are in attendance at your hearing today, learning and participating in the activities.

I've been selected as chairman of that task force and in the weeks ahead, we will carefully review NPPC's position in regard to the use of antibiotics in hog feed, taking into account any new evidence which has been made available so that we can recommend a current position to NPPC's leadership on this vitally important issue.

Until this task force has had an opportunity to evaluate the present status of the issue, I can only report that our position for the last 15 years—and that's roughly been the period of time that antibiotics have been under challenge from time to time. While no recent analysis has been undertaken concerning the economic consequences of a ban on the subtherapeutic use of antibiotics, some idea might be gleaned from a U.S. Department of Agriculture study of the—of the possible effects of a partial ban.

The study was conducted in 1978 at the request of the U.S. Senate Committee on Agriculture, Nutrition, and Forestry. It addressed proposed FDA restrictions on the use of tetracyclines and penicillin and a hypothetical restriction on the use of sulfa drugs for hogs.

According to the study, a partial ban could reduce pork output by as much as 17.8 percent for the first year. Assuming no change in imports, domestic production would increase in response to higher prices, but still fall short of a projected no-ban output level by nearly 1 to 3 percent after 5 years. Retail pork prices would increase by as much as 14.7 percent in the first year and fall to a 1- to 3-percent increase over a no-ban case after 5 years.

Pork producers will not be able to obtain former levels of production efficiency without undertaking some major adjustments. Until practical and affordable adjustment alternatives would be found, the economic costs of a partial ban would be borne by the Nation's consumers in the early years in the form of higher prices, and to a greater extent, by producers with the passage of time.

Mr. Chairman, the Nation's pork producers are a responsible group of citizens. They and their families are a major consumer of livestock products. They obviously would halt any practice that might endanger the lives of themselves and members of their family. This is the greatest assurance I know to the general public that the livestock producers of this Nation will respond positively and immediately to any scientifically valid threat to the Nation's food supply.

In conclusion, if the latest studies in this subject have failed to add any significant new supporting data to the possibility of health hazards from the use of antibiotics in animal feed, the Nation's pork producers should not be required to forgo the use of these valuable production tools that improve the efficiency of pork production.

On the other hand, should a thorough scientific review of the available research cause the U.S. Food and Drug Administration to conclude that some antibiotics should be curtailed or eliminated in

animal feed use, the Nation's pork producers will, of course, quickly comply.

Thank you, Mr. Chairman, for this opportunity to testify on this important issue representing our pork producers.

[The prepared statement of Mr. Wehler follows:]

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NATIONAL PORK PRODUCERS COUNCIL

STATEMENT TO THE

U.S. HOUSE OF REPRESENTATIVES COMMITTEE
ON SCIENCE AND TECHNOLOGY

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

ON ISSUES RELATING TO DEVELOPMENT OF RESISTANCE
TO ANTIMICROBIAL DRUGS

BY

MIKE WEHLER, PORK PRODUCER
PLAIN, WISCONSIN

DECEMBER 18, 1984

NATIONAL PORK PRODUCERS COUNCIL

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U.S. HOUSE OF REPRESENTATIVES COMMITTEE
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SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

ON ISSUES RELATING TO DEVELOPMENT OF RESISTANCE
TO ANTIMICROBIAL DRUGS

Mr. Chairman:

My name is Mike Wehler. I am a pork producer from Plain, Wisconsin. I represent Wisconsin pork producers on the Board of Directors of the National Pork Producers Council (NPPC). The NPPC and its 38 affiliated state associations represent over 110,000 pork producers. The national organization represents most of the commercial pork producers in the United States. Some of our members are large operators, raising as many as 50,000 hogs a year. The majority are mid-sized operators, while others are relatively small farmers who may produce a limited number of feeder pigs each year. In any case, we believe that the National Pork Producers Council represents the grassroots pork producer in the United States.

Pork producers are at least as concerned as any other segment of the population about the health and well-being of our fellow citizens. When there is a problem involving hog production methods, the nation's pork producers, through their organization, the NPPC, work closely with government agencies and others to correct that problem. Most recently, NPPC has been aggressively involved with the USDA and FDA in a producer information program aimed at reducing the frequency of high sulfa residue levels in pork products.

The NPPC Executive Committee recently established a producer task force to study the use of antibiotics in pork production. I have been selected as chairman of that task force. In the weeks ahead, we will be carefully reviewing NPPC's position in regard to the use of antibiotics in hog feed, taking into account any new evidence which has been made available, so that we can recommend a current position to NPPC's leadership on this vitally important issue. Until the task force has had an opportunity to evaluate the present status of this issue, I can only report what has been the position of the NPPC for the last 15 years. That is roughly the period in which the use of antibiotics in feed has been under challenge from time to time.

When the U.S. Food and Drug Administration proposed over seven years ago to restrict the use of tetracyclines and to ban the use of penicillin in feed, the NPPC, along with other industry organizations, requested additional study to scientifically validate whether there was any real cause for public alarm.

Antibiotics, in fact, are important tools in the modern production of pork. If these tools were removed from usage, it would undoubtedly increase the cost of production, but perhaps more significantly, the cost of pork to the average consumer.

While no recent analysis has been undertaken concerning the economic consequences of a ban on the subtherapeutic use of antibiotics, some idea might be gleaned from a U.S. Department of Agriculture study of the possible effects of a partial ban. The study was conducted in 1978 at the request of the U.S. Senate Committee on Agriculture, Nutrition and Forestry. It addressed proposed FDA restrictions on the use of tetracycline and penicillin and a hypothetical restriction on the use of sulfa drugs for hogs.

According to the study, a partial ban could reduce pork output by as much as \17.8 percent the first year. Assuming no change in imports, domestic production would increase in response to higher prices, but still fall short of a projected no-ban output level by 1 to 3 percent after five years. Retail pork prices would increase as much as 14.7 percent in the first year and fall to 1 to 3 percent over the no-ban case after five years.

Pork producers will not be able to attain former levels of production efficiency without undertaking some major adjustments. Until practical and affordable adjustment alternatives would be found, the economic costs of a partial ban would be borne by the nation's consumers in the early years in the form of higher prices, and to a greater extent, by producers with the passage of time.

The NPPC has, in the past, opposed any restrictions or ban on the use of antibiotics in feed. All of the scientifically-verified evidence we have seen so far would seem to indicate that the practice does not represent a significant hazard to public health and that there is no scientific basis to curtail the use of antibiotics in hog feed.

The principle focus of this hearing is the most recent research findings by the Center for Disease Control and the research contracted by the U.S. Food and Drug Administration in the Seattle-King County, Washington area. A number of responsible scientists have been quoted publicly as saying that neither study has added any significant new data to the possibility of health hazards from the use of antibiotics in animal feed. In other words, there seems to be considerable doubt in the scientific community itself that the so-called "smoking gun" has really been discovered in this issue.

Mr. Chairman, the nation's pork producers are a responsible group of citizens. They and their families are major consumer-users of livestock products. They obviously would halt any practice that might endanger the lives of themselves and members of their family. That is the greatest assurance I know to the general public that the livestock producers of this nation will respond positively and immediately to any scientifically-valid threat to the nation's food supply. Having said that, it naturally follows that should firm evidence be developed that

links the subtherapeutic use of antibiotics in feed to an adverse effect on human health, pork producers would immediately halt the practice and hope that the pharmaceutical companies would develop effective alternatives to take their place.

Mr. Chairman, the two antibiotics that have been proposed to be either banned or restricted are commonly used in hog feed. The proposed restrictions are essentially the same as were adopted in the United Kingdom about 15 years ago, and since then by a number of other European nations. All of the information we have seen would indicate that those restrictions have had little or no effect. In fact, the total use of antibiotics in European countries has remained rather constant. In some instances, it has increased.

In conclusion, if the latest studies on this subject have failed to add any significant new supporting data to the possibility of health hazards from the use of antibiotics in animal feed, the nation's pork producers should not be required to forego the use of these valuable production tools that improve the efficiency of pork production. On the other hand, should a thorough scientific review of all the available research cause the U.S. Food and Drug Administration to conclude that some antibiotics should be curtailed or eliminated in animal feed use, the nation's pork producers will, of course, quickly comply.

Thank you, Mr. Chairman, for this opportunity to testify on this important issue on behalf of the nation's pork producers. If you have any questions, I will gladly attempt to answer them. Thank you.

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Mr. GORE. Thank you very much.

You talk about that task force. What is the membership of the task force?

Mr. WEHLER. Membership of the task force is made up of seven people. Three of those people are producers who have been involved in the antibiotic issue over the past and then some scientific and university help in the—those difficult questions that we don't have the knowledge to address.

Mr. GORE. So the other four people are scientists?

Mr. WEHLER. No, two of—two of those people would be scientists.

Mr. GORE. And the other two?

Mr. WEHLER. One of those—excuse me, I said three producers. Four of those would actually be pork producers. Two would be scientists and the last one escapes me at present at to what that person would be. I can find that out and make it available to you, though.

Mr. GORE. All right. When is the task force due to complete its evaluation of the issue?

Mr. WEHLER. Mr. Chairman, we think that the—this issue has been an ongoing issue for 15 years. As a task force, we're just beginning to gather the information and bring ourselves up to date, since 1977, 1978 period of time.

At present, I don't know when we will complete that because I suspect that this will be an ongoing issue for a—some period of time into the future.

Mr. GORE. OK, so you don't plan—do you plan a report?

Mr. WEHLER. We would—Mr. Chairman, we would be most happy to share any report that our task force comes to with this committee.

Mr. GORE. All right, now, you come up with this figure of 14.7 percent increase in the cost of pork, what is that figure based on?

Mr. WEHLER. Mr. Chairman, that figure is based on a 1978 study by the—the—that the U.S. Senate Committee on Agriculture, Nutrition, and Forestry conducted, assuming that there was a—a partial ban on the use of tetracyclines and penicillin.

Mr. GORE. That—that—that study assumed that sulfa would be banned as well, didn't it?

Mr. WEHLER. I believe that's correct, Mr. Chairman.

Mr. GORE. Well, so that figure's not really relevant to a proposal that is aimed just at penicillin and tetracycline.

Mr. WEHLER. Well, Mr. Chairman, ASP250 is the product that pork producers commonly use in their grower feeds, which is a combination of penicillin, tetracycline and sulfa, so I suspect it would be difficult to separate that information.

Mr. GORE. Isn't there a—isn't there some idea that a two-element compound would be just as effective as a three-element compound?

Mr. WEHLER. Mr. Chairman, there is some indication and there are some pork producers who are using two-element compounds at this time that weren't back when the study was being conducted.

Mr. GORE. OK. So—so—I mean, I'm getting the impression that that figure—well, normally one would take a figure like that with a grain of salt anyway just because of the kind of information that both sides are dealing with, but if it—if it was based on elimination of all three of these drugs and doesn't take into account substitution of alternatives, then—then that—that price increase is probably not relevant to what would really happen if the FDA went forward with its proposal.

Mr. WEHLER. I—I guess I would agree, Mr. Chairman, there's probably very little relevant on the farm today that was relevant 7 or 8 years ago——

Mr. GORE. Yeah.

Mr. WEHLER [continuing]. As you are well aware.

Mr. GORE. Yes, sir.

Now, Dr. Ahmed—am I pronouncing that right?

Dr. AHMED. Correct.

Mr. GORE. And Ms. Chasis, you state that you've got some numbers in your testimony, too, here, and you've calculated that there are 116 Salmonella deaths each year associated with subtherapeutic use of antibiotics. Think we ought to take that one with a grain of salt, also?

Dr. AHMED. Well, these are estimated risks and they are obviously subjected to uncertainties in terms of the actual data that one uses and also the assumptions one makes. So we should take any risk estimates that are made with certain amount of caution.

Mr. GORE. Well, you make the statement that 69 percent of reported Salmonella outbreaks involving antibiotic-resistant strains are traceable to animal sources. What's that based on?

Dr. AHMED. That's from the CDC study that was published in Science. That was done by Dr. Holmberg and Dr. Cohen.

Mr. GORE. Uh-huh. Now, on page 5 of your statement, you use another method to determine the risk and arrive at a number of 264 deaths——

Dr. AHMED. Right.

Mr. GORE [continuing]. Annually from infections by resistant strains from subtherapeutic use of penicillin and tetracycline. That's double your first estimate—a little more than double your first estimate. How accurate—which—which is—which is the one that you think is accurate?

Dr. AHMED. Mr. Chairman, because of the uncertainties, we decided to do it two ways: One, by starting out by looking at the actual incidence of Salmonella, then using the 4.2 fatality rate——

Mr. GORE. Uh-huh.

Dr. AHMED. Now you must remember, that number was derived from reported cases, all right, so it has to be—there's a certain amount of uncertainty as to how it would apply across the board.

The other was to start out by looking at the actual number of deaths reported in this from Salmonella——

Mr. GORE. Yes.

Dr. AHMED [continuing]. And then try to make some estimation of how many deaths could be attributed by using the same set of assumptions and ratios. So we come up with—but it's in the same order of magnitude, and in doing risk assessment when you are within an order of magnitude one does extremely well. If you look at cancer assessment, you're sometimes off by six orders of magnitude, Mr. Chairman

Mr. GORE. Yes, I'm familiar with that and, in fact, those numbers are quite close for——

Dr. AHMED. That's right.

Mr. GORE [continuing]. For work of this kind.

Now, on page——

Dr. AHMED. We get the numbers in terms of a range from 100 to 300.

Mr. GORE. Yes; on page 10, the various alternatives to penicillin and tetracyclines are listed, and you indicate that some are considered excellent substitutes. How do these substitutes compare in cost with antibiotics now in use?

Dr. AHMED. In terms of what, cost?

Mr. GORE. Uh-huh.

Dr. AHMED. We haven't done a study on the cost, Mr. Chairman. We haven't really looked at what they may be in terms of even efficacy. All we have is some studies that have been reported. For example, the OTA did a study not too long ago, and some other studies that they cite, that indicate that these antibiotics exist and that they can be used in the animal feed industry——

Mr. GORE. Yeah.

Dr. AHMED [continuing]. And some of them are actually being used, in, we understand, for example, the poultry industry. Bambermycin, I believe, is being used.

Mr. GORE. Yes, yes, I've read about that.

Dr. AHMED. So that it's not a question of—the point we're trying to make here, Mr. Chairman—to suggest that alternatives do exist in the industry.

Mr. GORE. Yes; what is your reaction to the criticisms of the Holmberg, Cohen et al. study? You've heard them this morning and on this panel. What's your reaction——

Dr. AHMED. My reaction is——

Mr. GORE [continuing]. To those criticisms.

Dr. AHMED [continuing]. That I think I can—I agree with Dr. Cohen that there were certain factors in the studies that could have been—if you did the study prospectively—if you were to design and try to trace it, you would have followed the meat supply all the way from the point of production to point of consumption. Since the study was restrospective, you have to draw certain inferences, and I think, from discussing this issue with independent scientists, it's quite clear that the—as you mentioned earlier—circumstantial evidence is extremely strong and there are obviously certain points, for example, not having a sample of the actual meat consumed, the fact that we have a plasmid from a dairy calf in an adjacent feedlot does indicate a certain missing—a certain gap in the information.

However, if everything is put together in the proper—in the total picture, I don't think you could get a better set of evidence to show the linkage between the cause and effect here for this kind of study.

So I don't think that the objections or the weakness in the studies and in any way serious and that they should be taken as a whole as providing very strong evidence.

Mr. GORE. Uh-huh.

Dr. Bonner, why have cattle producers abandoned the use of penicillin as a feed additive?

Dr. BONNER. To my knowledge, penicillin was never used as a feed additive in cattle.

Mr. GORE. Why?

Dr. BONNER. Beats me. [Laughter.]

Mr. GORE. OK, that's fair enough.

Anybody else know the answer to that?

Mr. Gustafson, do you——

Dr. GUSTAFSON. Well, it was never registered for use in cattle and why it was never registered is speculation. You'd have to know a little bit about the history of it, I suppose.

Mr. GORE. Dr. Bonner, in what situations is the use of tetracycline in cattle essential?

Dr. BONNER. In several large areas scattered over the United States, one of the most devastating and economically significant diseases in cattle is anaplasmosis, and the tetracyclines are the only products that are effective in controlling and treating this disease.

Mr. GORE. There are no substitutes for it?

Dr. BONNER. There are no substitutes, and also, there are no substitute feed additives that are significantly effective against the respiratory problems that perhaps produce as many as 90 percent of the deaths in confinement feedyards.

Mr. GORE. Uh-huh. All right.

Mr. Klinger, what percentage of livestock and poultry producers rely entirely on a commercial source of feed for their animals? Do you know the answer to that?

Mr. KLINGER. Our statistics are difficult to come by because of the magnitude and complexity of our industry. A manufacturer may comply—or supply a complete feed; may supply components at the country elevator level, which sometimes we call dealers; they may supply units or complete feed. Over the years, particularly the last decade, there's been quite a trend to producers building their own feeds in part. Even the largest producers may buy a commercial feed, for example, to obtain pelleted starters and then go and build their own feeds from the ground up.

Mr. GORE. You don't know the answer to it?

Mr. KLINGER. I don't think any of us do.

Mr. GORE. Fine; what percentage of commercial feeds sold are medicated feeds?

Mr. KLINGER. Again, this will be opinion because it can be qualified as to the type of species or feeding, but in general, I would say 60 percent, but of course, in poultry feeds, you may get as high as 100 percent, down to other species where it might be 5 or 10 percent.

Mr. GORE. What percentage of livestock and poultry producers mix their own medicated feeds? Again, that's something we probably don't know?

Mr. KLINGER. It's not an all or nothing. Again, let's take a pork producer who may start off with a commercial, pelleted, medicated feed and then go to what we call grind and mix or building their own feeds. I would say that probably 60, 60 percent of the swine, for instance, are fed by feed that's mixed on the farm.

Mr. GORE. OK.

Dr. Gustafson, what percentage of the antibiotic drugs sold for veterinary use are used for subtherapeutic purposes and what percentage for therapeutic purposes?

Dr. GUSTAFSON. Again, it varies from species to species. I think currently in poultry, the overwhelming use of tetracyclines, for example, is at therapeutic levels. In swine, I would say that most antibiotics are used at what are considered subtherapeutic levels. It's difficult to put an overall percentage on these figures.

Mr. GORE. If you could supply any additional information you have on that for the record, we'd appreciate it.

Dr. GUSTAFSON. Yes, certainly.

[The information follows:]

CYANAMID

American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08540
(609) 799-0400

January 24, 1985

Ms. Elizabeth Eastman
Subcommittee on Investigations and Oversight
822 HOBA #1
Washington, D.C. 10515

Dear Ms. Eastman:

As part of my testimony at Mr. Gore's hearings on December 8, 1984, I indicated that I would try to obtain annual industry wide figures on separate categories of antibiotic use. The attached are rough estimates of kilograms of antibiotic use annually in the categories of disease prevention and growth promotion (both subtherapeutic as well as therapeutic).

Very truly yours,

Richard H. Gustafson

Richard H. Gustafson, Ph.D.
Associate Research Fellow

/naf
Attachments

TETRACYCLINE CTC/OTC

	Therapeutic	Sub-Therapeutic		
		Disease Prevention	Growth Promotion	Total
	KKG	KKG	KKG	KKG
Cattle	50	589	130	69
Swine	30	950	701	1,681
Poultry	187	33	—	220
Total	267	1,572	831	2,670

Source: IMS, AHI Est.

ALL ANTIBIOTICS

	Therapeutic	Sub-Therapeutic		
		Disease Prevention	Growth Promotion	Total
	KKG	KKG	KKG	KKG
Cattle	458	1,100	340	1,898
Swine	250	3,578	1,391	5,219
Poultry	304	580	315	1,199
Total	1,012	5,258	2,046	8,316

Source: IMS, AHI Est.

KKG'S BASED ON RATIOS OF SALES

Mr. GORE. How much penicillin and tetracycline is sold, compared to other antibiotics, for use in livestock and poultry?

Dr. GUSTAFSON. I think there's a lot of tetracycline used in all three major meat species. In poultry, for example, as you've heard, the ionophore coccidiostats are an important additive and are used virtually in all poultry.

In cattle, as you've heard, not too much tetracycline is used. In swine, quite a bit is used. The swine product that's used most often is a combination of tetracycline, penicillin, and sulfa.

If tetracyclines are withdrawn from the market because of evidentiary hearings and a final rulemaking, sulfa would go, too, because it's part of the product.

Mr. GORE. Unless there was a new compound that——

Dr. GUSTAFSON. Unless a new product with sulfa contained in it were registered.

Mr. GORE. Yeah, yeah. Has one been proposed?

Dr. GUSTAFSON. Not to my knowledge, no.

Mr. GORE. Uh-huh. Has one been informally proposed?

Dr. GUSTAFSON. No.

Mr. GORE. All right, well, I have some other questions, but I want to recognize my colleague, Mr. Volkmer, and recognize him for questions at this time.

Mr. VOLKMER. I'm not trying to be facetious, Mr. Chairman, but I would like to ask Dr. Ahmed if he's ever had a farm, operated a farm, livestock, or anything, or had anything to do with livestock other than——

Dr. AHMED. I lived for 10 years in Minnesota and I visited a lot of farms there, so I've never operated one, but I've known dairy cow farmers and I've been there and I visit them and I'm very interested in the farming sector.

Mr. VOLKMER. The reason I ask that basically is because in your testimony you allude to another method of reducing the incidence of disease in farm animals would involve altering farming practices and then you go on to say maybe we should do away with feedlots; maybe we should reduce the number of—basically, that's what I read into it——

Dr. AHMED. Yes.

Mr. VOLKMER [continuing]. And also on our pork production where we have confinement, we shouldn't have that, but should have bigger, open space and things like that.

Dr. AHMED. Well, we don't go in that much detail.

Mr. VOLKMER. I know, but——

Dr. AHMED. But we do certainly suggest that—and we have contact with a lot of people who are concerned about the present way of raising in terms of quarters and nonhygienic conditions, that there can be more—there could be other ways of animal husbandry than the way we raise animals today.

I'm not saying that they're necessarily the most economical way of raising animals, nevertheless, animals are confined. I know, for example, in the pork industry—in the swine industry, the animals are confined quite often.

Mr. VOLKMER. But it's an economical way to do it.

Dr. AHMED. Well, that's the other side of the question, as other witnesses have alluded to. It may be, but it may be not the most humane way of raising animals.

Mr. VOLKMER. Now—well, I don't want to go on to humane aspects. [Laughter.]

Dr. AHMED. Well, I think you should care about animals——

Mr. VOLKMER. We could sit here all day and I'll argue with——

Dr. AHMED. I'm not going to be arguing on behalf of the Animal Welfare Society, but I'm sure they're concerned about this issue, too.

Mr. GORE. Well, I'd appreciate it if you wouldn't because that could get us into a long argument because I don't believe, you know, in all the arguments of the Animal Welfare Society, either.

Dr. AHMED. No, but I'm just speaking for myself. I've been to—I've been to these farms and I've seen how animals are confined.

Mr. VOLKMER. Yeah. But on the other hand, the American public eats cheaper and better than anyplace else in the world in percentage of our disposable income.

Dr. AHMED. Well, I'd like you to give me the figures on that, sir.

Mr. WEHLER. Mr. Volkmer——

Mr. VOLKMER. Fifteen percent of their disposable income.

Mr. WEHLER. As a pork producer, I guess I would like to respond just very briefly that my hip boots wore out about 15 years ago as I was wading around in the mud to feed those pigs outside and I think the efficiency of some of the confinement operations we have today has contributed greatly to lower priced red meat for our consumers.

Mr. VOLKMER. And many of those are a lot cleaner than what you had before when you had just the old outlot out there and they're grubbing in the mud and eating slop, too.

Mr. WEHLER. And 20-degree-below-zero weather we sometimes have in Wisconsin.

Dr. AHMED. I think we're getting off the topic of my expertise. [Laughter.]

I cannot speak to this issue——

Mr. WEHLER. You brought it up.

Dr. AHMED. What can I say, I was asked the question.

Mr. VOLKMER. All right, you mentioned availability of alternatives for tetracycline and penicillin for use in livestock, and I believe in your testimony, you say, for example, tylosin——

Dr. AHMED. Tylosin, right.

Mr. VOLKMER [continuing]. Tylosin and bac—what is it?

Dr. AHMED. Bacitracin.

Mr. VOLKMER. Bacitracin are considered excellent substitutes for tetracyclines and penicillin in swine, chicken and turkey. Have those been used?

Dr. AHMED. Excuse me, I'm trying to see where you're referring to.

I believe they have been. In fact, in our petition, we have a little more detailed information——

Mr. VOLKMER. I find this on page 19——

Dr. AHMED [continuing]. References and so on.

Mr. VOLKMER [continuing]. And it says, "In the case of pork and beef, tylosin and bacitracin are considered viable substitutes."

Ms. CHASIS. If I may respond, this—these statements were based on a study that was done by Mr. Headly for, as part of an OTA study, and those—that language is taken directly from his analysis of the viability of substitutes for tetracycline and penicillin.

Mr. VOLKMER. OK. So you're just taking somebody else's word for it?

Dr. AHMED. That's right.

Mr. VOLKMER. So be it.

Now I'd like to ask——

Dr. AHMED. We took a lot of words of other scientists, by the way, too. We didn't do any of this research ourselves.

Mr. VOLKMER. Well, Dr. Bonner, what about the—you've already alluded to the question of respiratory disease in beef cattle and would either one of these that he's mentioned be effective?

Dr. BONNER. If anybody claims that they're effective, they've never tried to raise cattle when it's zero degrees and a foot of snow.

No, sir; you're referring to bacitracin and tylosin?

Mr. VOLKMER. Yes, that's correct.

Dr. BONNER. No, sir, these products are not effective. Bacitracin is not absorbed from the intestinal tract.

Mr. VOLKMER. All right.

Mr. Wehler, what about pork production? Have you known of anybody to use tylosin and bacitracin?

Mr. WEHLER. Yes, those products are used in pork production.

Mr. VOLKMER. Are they equivalent to a substitute for the sulfa pencillin and tetracycline?

Mr. WEHLER. Definitely not; in my opinion.

Mr. VOLKMER. Dr. Ahmed, do you have any other substitutes?

Dr. AHMED. Could I ask a question of the gentleman we just——

Mr. VOLKMER. It's up to the chairman.

Mr. GORE. Well, that's not our normal procedure, but we'll allow that.

Dr. AHMED. I just want a clarification. When you say it's not as good, you mean economically or you mean in terms of efficacy?

Mr. WEHLER. Both.

Mr. VOLKMER. Now, Dr. Ahmed, do you have any other substitutes?

Dr. AHMED. As I said, our purpose of presenting this information is to suggest that there are alternatives and we will be doing more studies on this, but we have not undertaken at this time to give you a line-by-line study of the industry to suggest what substitutes are available, what could be used.

We also recognize that different industries have different problems. There are obviously in the poultry industry a lot more substitutes for tetracycline and penicillin, at least subtherapeutically? It's available today and they're being used today.

We know for example, one of the largest poultry manufacturers—producers in this country, Perdue Chicken does not use any penicillin and tetracycline in growing their products at all. And so, obviously, they have an adequate substitute.

Ms. CHASIS. I just want to add that our petition is directed at subtherapeutic uses of penicillin and tetracycline, and therefore, if it were accepted, it would not affect treatment of disease at therapeutic levels of penicillin or tetracycline.

Mr. VOLKMER. I understand that.

Dr. Gustafson, do you wish to comment?

Dr. GUSTAFSON. Yes; I think when we—when we talk about Perdue and why they're not using tetracyclines, we can speculate, but we should have to remember what Dr. Hays told us. He reminded us that since the ionophore coccidiostats were registered in the early 1970's, there have been no registrations allowed for combination with the ionophores and tetracyclines.

I think it's fairly obvious that the reason tetracyclines are used less at subtherapeutic levels now is because there are no registrations with the ionophores. They're used much more at higher levels now, as a matter of fact.

Mr. VOLKMER. Ionophores are used basically for growth, not——

Dr. GUSTAFSON. The ionophores in poultry are used for the control of coccidiosis.

Mr. VOLKMER. Right.

Does anyone wish there to comment on the King County-Washington/Seattle study that was done?

Dr. GUSTAFSON. Well, beyond what I mentioned in my testimony, I think it—I think I have to say to the FDA that they did an excellent job of finding some competent scientists. My only concern is that if this—indeed, this is the study that's to be used to decide policy issues on the continuation of the use of subtherapeutic antibiotics, it simply doesn't answer that question.

I think there are other studies that could be done and they were mentioned by the National Academy of Sciences. Nevertheless, the epidemiological study on Campylobacter is very important to our knowledge of this organism.

Mr. VOLKMER. Yes, but that would seem to show that the—what was it, Camp——

Dr. GUSTAFSON. Campylobacter, yes.

Mr. VOLKMER [continuing]. Campylobacter seemed to be more prevalent, at least in that study, than the—the Salmonella.

Dr. GUSTAFSON. Yeah. I think—I think that's generally regarded as true, that Salmonella diarrheas are less frequently seen than Campylobacter diarrheas in humans in the United States and other countries also. I think our CDC people here would agree to that.

Mr. VOLKMER. Dr. Ahmed, is it your position, or your all's position in filing the petition that if subtherapeutic uses of antibiotics were curtailed, that the problem of Salmonella infection would go away?

Dr. AHMED. No, I don't think we—we state that. We do know that when you have some antibiotic strain—resistant strain of Salmonella, the death rate is 21 times more than nonresistant strains. What that may be due to, we don't really know right now, but we do know that the death rate is much, much higher.

We believe that if the resistance of these strains is removed, perhaps you won't have this high a rate of fatality.

Mr. VOLKMER. My problem with what you said, Dr. Ahmed, if I may inject——

Dr. AHMED. Yes.

Mr. VOLKMER [continuing]. Is the word "perhaps."

Dr. AHMED. Well, we—when I say anything, we have to take all this information with a certain amount of caution, as I mentioned earlier. None of the guesstimates can be made definitive. And when I say "perhaps," I meant that there are very good reasons to believe that this will be the case.

Mr. VOLKMER. But it's not necessarily so.

Dr. AHMED. I would say pretty close to necessarily so.

Ms. CHASIS. If I may respond, the imminent hazard provision, as interpreted by FDA through application, and decisions, and through proposed rules, contemplates a showing of significant likelihood of substantial harm to the public health or animal health, and it's that criterion we've used as a basis for our petition.

Mr. VOLKMER. But there's no question that even under the proposed order from FDA and even under your petition and on the testimony here today that we will continue to have therapeutic use of the same antibiotics.

Ms. CHASIS. Our petition does not seek a ban on therapeutic uses; that's correct.

Mr. VOLKMER. And if we're really worried about the hormone or the antibiotic-resistance factor and the development of that, not only in animals, but transmitted to humans, et cetera, you're still going to have that; are you not? Anybody—if you still use the therapeutic, are you still not going to have the same problem with it?

Dr. GUSTAFSON. Subtherapeutic uses and therapeutic uses select for resistant bacteria. If we do away with the lower level uses, I assume the therapeutic levels will still select for resistant organisms and the animal——

Mr. VOLKMER. And would you not, if you didn't have this subtherapeutic level use, have a better chance—or get back to perhaps, have more disease in the animals as they—from—in other words, birth, and early stages on up?

Dr. GUSTAFSON. Yeah; that's probably true and that's the assumption, I think, that Dr. Hays mentioned this morning, that a reduction in the use of subtherapeutic antibiotics would inevitably require a—a use at higher levels and the treatment——

Mr. VOLKMER. You'd have an increased use at higher levels——

Dr. GUSTAFSON. Yes.

Dr. AHMED Would you not?

Dr. GUSTAFSON. Yes.

Mr. GORE. Would the gentleman yield?

Mr. VOLKMER. And I'm wondering what effect that's going to have on this same resistance factor, bacterial resistance factor. Is that going to possibly increase the—I don't—yes, I'll yield.

Mr. GORE. I think these are all good questions. I'm wondering—I tried to get a feel earlier for the percentages and my impression is that at the current time, about 80 percent of animal antibiotic use is subtherapeutic and about 20 percent is therapeutic, even if you grant that there might be some increase in therapeutic usage if subtherapeutic use of these particular—these two substances were cut back—still there would be a dramatic decrease in the evolutionary pressure put on the selection of resistance genes; would there not?

Dr. GUSTAFSON. I think that it depends on the number of animals that would be receiving therapeutic uses of antibiotics. I think in the poultry industry, we've seen an increase in the use of therapy. We have to also consider the uses—other uses. Injectibles in pork, and pigs, and cattle, and in water in——

Mr. GORE. But do you——

Dr. GUSTAFSON [continuing]. Poultry.

Mr. GORE. But do you generally accept that 80 percent/20 percent breakdown? Is that roughly accurate?

Dr. GUSTAFSON. I think that—if we think about the figures on economy that were related by the Animal Health Institute last spring—I'm trusting my memory now—it seems to me that the feed additive uses accounted for about $280 million use at the—at the producer level, and the nonfood additive market size was about $210 million.

So it means that they're probably 40/60——

Mr. GORE. Well——

Dr. GUSTAFSON [continuing]. If you can use dollars as an—as an estimate.

Mr. GORE. Can you?

Dr. GUSTAFSON. Probably not, but I don't know what else we can use.

Mr. GORE. OK.

I thank my colleague for yielding.

Mr. VOLKMER. I'd just like—I'm sorry I wasn't—I had to go to another meeting, that's why I didn't get all the testimony and I haven't had an opportunity since I've been out in the district—just flew in this morning—to have an opportunity to read it before, so if you have, just tell me you have and I'll have to check my staff or the committee staff.

Dr. Bonner, have you estimated—or the National Cattlemen's estimated—any economic cost to livestock beef production in the event that the FDA does enter the order as proposed?

Dr. BONNER. No, sir, we have not. It's only that—either the NAS report or the CAST report where they alluded that in the first year, there would be a $3.5 billion cost, either to the livestock producers or the consumers through increased cost of production or decreased availability of product.

Mr. VOLKMER. And increased cost, too, and this would continue over a period of years, would it not?

Dr. BONNER. This is per year.

Mr. VOLKMER. Yeah.

Dr. BONNER. No doubt over a period of years, there would be other products that might replace some of that.

Mr. VOLKMER. Does anyone else—Mr. Wehler, do you have anything on pork production?

Mr. WEHLER. Only what's in my testimony——

Mr. VOLKMER. Fine.

Mr. WEHLER [continuing]. And the chairman and I discussed that at length a little earlier.

Mr. VOLKMER. I've had some——

Mr. WEHLER. I'd be glad to go over that again—page 3 of my testimony refers to a report called for by the—the Senate Committee on Agriculture, Nutrition, and Forestry dealing with a partial ban

on tetracyclines and penicillin, and they indicated that back in 1978, the first year could be as much as a 17.8-percent reduction in pork, which admittedly is old information at this point in time.

Mr. VOLKMER. I've been—I don't know, maybe we can find out for sure on this and provide it for myself, Mr. Chairman, that possibly if you had a ban as proposed, there would be in the second year a reduction in the real disposable income in the country of $5.1 billion and an increase in food bills annually $3.5 billion.

Thank you, Mr. Chairman.

Mr. GORE. Thank you.

We're going to continue this hearing tomorrow and there will necessarily be some overlap because several of the witnesses tomorrow have a substantial amount of expertise on the topic we've discussed today, but we're trying to keep the focus on the larger topic of antibiotic resistance.

Mr. VOLKMER. Mr. Chairman.

Mr. GORE. Yes.

Mr. VOLKMER. I did—because I don't know if any of these have it—I posted up on the previous panel—did you all in your statements address—or any of you—the Animal Health Institute study that's going on? If not, I'd like—if any of you know about it—tell us.

Dr. GUSTAFSON. Yes; I mentioned it, but I didn't go into any detail on it.

Mr. VOLKMER. When—do you have any idea about when it would be completed?

Dr. GUSTAFSON. It's scheduled to be completed about 10 months from now, next fall, fall of 1985.

Mr. VOLKMER. So it could not be in consideration of anything right now at the present time if FDA decides to proceed?

Dr. GUSTAFSON. If they have to make their decision right now, no.

Mr. GORE. I'd like to——

Mr. VOLKMER. Excuse me—now that study goes in—does it go into the resistance—bacteria-resistance factor——

Dr. GUSTAFSON. Yes, it does.

Mr. VOLKMER [continuing]. Use of antibiotics——

Dr. GUSTAFSON. Yes, it's an epidemiological study in humans.

Mr. VOLKMER. So it would be pertinent to the question?

Dr. GUSTAFSON. Yes, definitely.

Mr. VOLKMER. Thank you.

Mr. GORE. I'd like to thank all of our witnesses today and apologize for the length of these proceedings, but the subject matter is tough and we just have to wade through it and it takes a little time, so thanks for your patience and now we can all go get something to eat of our respective choices, but thank you all for your testimony and we will—we will go back into session at 9:30 tomorrow morning here in this same room.

[Whereupon, at 2:40 p.m., the subcommittee was adjourned, to reconvene at 9:30 a.m., Wednesday, December 19, 1984.]

ANTIBIOTIC RESISTANCE

WEDNESDAY, DECEMBER 19, 1984

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT,
Washington, DC.

The subcommittee met, pursuant to call, at 9:30 a.m., in room 2325, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Mr. GORE. The subcommittee will come to order.

I'd like to welcome all of our witnesses and guests to this second day of hearings on the subject of antibiotics and antibiotic—antibiotic resistance. Yesterday we focused on the subtherapeutic uses of antibiotics for growth promotion in livestock feeds. We heard from distinguished scientists, regulators, and a variety of interest groups. They discussed the value of antibiotics in animal production and health, as well as concerns about promoting the development of bacteria resistant to antibiotics. The information presented at yesterday's hearing was diverse and complicated. Clearly all those present, no matter what their position, were concerned about the safety of the food supply and the well-being of consumers. What was less clear was the extent to which antibiotics fed to livestock represent a danger to public health.

There was a consensus that the overuse or misuse of antibiotics contributes to the development of bacterial populations with antibiotic resistance genes. These genes are usually carried on small circular strands of DNA known as plasmids, and plasmids can be readily transmitted between different species of bacteria. Therefore, while most bacteria inhabiting animals are usually harmless to humans, there is the potential for animal bacteria to transmit their resistance genes, resistance plasmids, to other bacteria which are not harmless and which may in fact cause serious human illness. Where the consensus breaks down is in establishing whether this potential mechanism for developing resistant human pathogens represents a real threat or just a theoretical threat to human health.

Today we will take up the subject of antibiotic use in human medicine. While approximately one-half of the antibiotics used annually in this country are administered to animals, the other half is prescribed by physicians for human beings. The same selective pressure on bacteria to develop resistance is therefore operating in the human population. In today's proceedings, we will explore the question of resistance produced by antibiotic use to treat patients in hospitals and physicians' offices. We will try to understand how

widespread the problem of resistance is, how drugs are actually used, and whether there is a danger that antibiotics will become ineffective to treat serious infectious disease. We also hope to hear ideas on what can be done about this problem from some of the most distinguished infectious disease specialists in the Nation.

To begin the day's proceedings, therefore, I'd like to welcome our first panel of experts who will discuss the scope of the resistance problem.

Our first panel of witnesses is made up of Dr. Stuart Levy, professor of molecular biology and microbiology at Tufts University School of Medicine in Boston; Dr. Jim Hughes, Director of the Hospital Infections Program for the Centers of Disease Control in Atlanta; and Dr. Michael Parry, director for infectious diseases and microbiology at Stamford Hospital in Stamford, CT.

Welcome to all three of you. We're delighted that you were willing to help us in this effort. Without objection, your entire prepared statements will be included in the record in full and, if you care to summarize any portion of your comments, feel free to do so.

Dr. Levy, we'll begin with you. You have been a leader in this whole area. And I believe you're president of this group that has been established on antibiotic use, and we're delighted to hear from you. So please proceed.

[The biographical sketch of Dr. Levy follows:]

CURRICULUM VITAE

Name: STUART B. LEVY

Date of birth: November 21, 1938

Place of birth: Wilmington, Delaware

Nationality: U.S.A.

Marital Status: Married

Education:

Williams College, Williamstown, Mass.	A.B. magna cum laude	1956-1960
University of Penn., Philadelphia		1960-1962
University of Penn., Philadelphia	M.D.	1963-1965

Positions Held:

Research Fellow, Dept. of Microbiol. Univ. of Milan	1962 - summer
Public Health Service Fellowship, Laboratoire Pasteur	1962-1963
Publiker Nutrition Fellowship, Kenyatta Nat.Hospital	1964 - summer
Research Fellow, Dept. of Microbiol. Keio Univ. Tokyo	1964 - autumn
Intern and Medical Resident, Mt. Sinai Hospital N.Y.	1965-1967
Res. Fellow, (part-time) Dept. of Cell Biol. Mt. Sinai Hosp.	1966-1967
Staff Associate, NIAMD, Nat. Inst. of Health, Bethesda	1967-1970
Visiting Prof., Dept. of Pathology, University of Padua, Italy	1970 - February
Fellow in Hematology, New England Med. Ctr., Boston	1970-1971
Collaborator, E. African Viral Inst., Enteobe, Uganda	1971 - spring
Asst. Prof. Medicine, Asst. Prof., Molecular Biology and Microbiology, Tufts University Med. School	1971-1975
Visiting Prof., Pasteur Institute, Paris	1976
Staff Physician, N.E. Medical Ctr. Hosp., Boston	1976-present
Staff Scientist, Cancer Res. Ctr., Tufts University	1976-present
Assoc. Prof. Medicine, Molec. Biol. & Microb., Tufts	1976-1980
Prof. Medicine, Molec. Biol. & Microb., Tufts Medical School	1980-present

Honors and Public Service:

Phi Beta Kappa	1960
Mary Ellis Bell Prize for Research	1964
Borden Undergraduate Research Award in Medicine	1965
Research Career Development Award	1972-1977
Fellow, American College of Physicians	1975
Leukemia Research Scholar of the Year (National Leukemia Association)	1975
Scientific Advisory Committee, Microbiology and Virology Study Section, Amer. Canc. Society Vice-Chairman, (1981); Chairman (1982)	1979-1983
Scientific Advisory Committee, NIH Plasmid Reference Center	1978
Research Committee, Medical Foundation, Inc., Boston	1980-1984
Editorial Board, Antimicrobial Agents & Chemotherapy	1981-1983
Consultant, Food & Drug Administration, Washington	
Scientific Advisor, Biomedical Research Center, Universidad Nacional Pedro Henriquez Urena, Santo Domingo, D. R.	1977-
Biohazards Committee (outside member) Boston Univ.	1980-
Co-organizer, The Open Circle	1978-
Co-organizer, International Plasmid Conference Santo Domingo, Dominican Republic	1981
Special Consultant, World Health Organization, SEARO	1981
Scientific Advisory Board, Natural Resource Defense Council, New York	1981-
Member, Governor's ad hoc Committee on Recombinant DNA industry in Massachusetts	
Scientific Working Group on Antimicrobial Resistance World Health Organization, Geneva	1981
Advisor, On the Fate of the Earth, Inc.	
President, The Boston Blood Club	1983-1984
President, Alliance for the Prudent Use of Antibiotics	1981-
1984 Overseas Visitor, Board of Postgraduate Medical Education, Royal Melbourne Hospital, Australia	
General Chairman, International Workshops and Conference on "The Use of Antibiotics Worldwide" (Fogarty International Center, NIH)	

University Service:

Chairman, Scientific Affairs Committee
Member, Biohazards Committee
Member, Radiation Safety Committee
Representative to Executive Council
Member, University Patent Committee

Societies:

American Association for Cancer Research
American Society of Biological Chemists
American Society for Clinical Investigation
American Society of Hematology
American Society for Microbiology
New York Academy of Sciences

Publications:

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Marshall, B., C. Tachibana and S. B. Levy (1983) Frequency of tetracycline resistance determinant classes among lactose-fermenting coliforms. Antimicrob. Agts & Chemo. 24:835-840.

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McMahon, G., J. L. Alsina and S. B. Levy (1984) Induction of a (Ca^{+2}, Mg^{+2})-dependent endonuclease activity during the early stages of murine erythroleukemic cell differentiation. Proc. Nat'l. Acad. Sci. (in press)

McMahon, G., J. L. Alsina and S. B. Levy (1985) (Ca^{+2}, Mg^{+2})-dependent endonuclease activity in different subpopulations of spleen cells from normal and erythroleukemic mice. Exp. Cell Res. (in press).

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Invited Editorials

Levy, S. B. (1974) Cat leukemia: A threat to man? New England J. Med. 290:513-514.

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Levy, S. B., R. C. Clowes and E. L. Koenig (eds.) (1981) Molecular Biology, Pathogenicity and Ecology of Bacterial Plasmids. Plenum Press, New York.

STATEMENTS OF STUART LEVY, M.D., PROFESSOR OF MOLECULAR BIOLOGY AND MICROBIOLOGY, TUFTS UNIVERSITY SCHOOL OF MEDICINE, BOSTON, MA; JAMES M. HUGHES, M.D., DIRECTOR, HOSPITAL INFECTIONS PROGRAM, CENTERS FOR DISEASE CONTROL, ATLANTA, GA; AND MICHAEL PARRY, M.D., DIRECTOR, INFECTIOUS DISEASES AND MICROBIOLOGY, STAMFORD HOSPITAL, STAMFORD, CT

Dr. LEVY. Thank you, Mr. Chairman.

I am Dr. Levy. I'm professor of medicine and of molecular biology and microbiology at Tufts University School of Medicine, and on the staff of the New England Medical Center Hospital.

Distinguished members, invited guests, and visitors, I am delighted to be here today. I've come to you as a clinician, medical scientist, and educator who's concerned about the problem of antibiotic resistance and its public health consequences. I believe that the therapeutic value of antibiotics is being eroded. Increasing numbers of resistant bacteria are causing infections in our communities and hospitals here and throughout the world.

These bacteria thwart our present-day ability to treat even common infections of the body. While the diseases themselves are not necessarily occurring more frequently, they are increasingly being caused by variant strains of common bacteria resistant to antibiotics previous effective in their cure. They lead to death, tissue damage, unnecessary hospitalizations, toxic side effects of substituted drugs, and increased costs. These bacteria know no geographic borders. More importantly, they are now significant components of man's everyday environment.

I see the phenomenal rise in resistant strains as the direct result of antibiotic use, misuse, and overuse in two major areas here and abroad, that is the therapy of man, and animals, and growth promotion in animals.

Resistant bacteria exist in all parts of our environment. They are delivered there and picked up from there by man, animals, and agricultural plants. These organisms quietly share the environment with us unless they enter the body where they can cause disease which the mainstay of treatment has always been—or at least in the last 40 years—antibiotics.

Moreover, as you are no doubt aware, most resistant strains transfer to other bacteria their resistance via small pieces of DNA, as the chairman indicated, called plasmids, and they can also exist on smaller units of DNA called transposons. Genes for resistance to most, if not all, antibiotics probably exist somewhere in nature, but their problem to human health varies with their frequency in that particular environment and the amount of antibiotic use there.

Early in their development, antibiotics were used primarily in hospitals which became havens for resistant bacteria. This has remained so and the problem has increased. In fact, new resistant pathogens have appeared in hospitals, and bacteria resistant to more than one drug are now common entities. Reports appear weekly of resistance problems in hospitals somewhere in the world. The inappropriate use of these drugs in hospitals has been addressed by Dr. Edward Kass and others who will be speaking to you today.

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A more recent development is the emergence of resistant strains outside the hospital. For example, meningitis and ear infections in children, pneumonias in adults, are often caused by Hemophilus influenzae. Previous to 1974, these infections were uniformly cured by ampicillin and by other drugs; now they are not, at least not a large percentage, or at least a significant percentage of them.

Two children from a Maryland community died within 2 days from meningitis because resistance was not discovered in time. Since this first report, multiple-resistant strains of Hemophilus have caused problems all over the world. Besides deaths and treatment failures, the existence of these resistant organisms necessitate costly diagnostic testing and higher priced, sometimes more toxic, antibiotics when they are available. Pneumococcal pneumonias are now presenting us the same problem.

Unfortunately, geographic location offers no protection. Penicillin-resistant Neisseria gonorrhoeae, the cause of gonorrheae, spread within months from Southeast Asia, to Europe, and the United States. These kinds of highly resistant bacteria now exist in more than 60 countries of the world. This example shows that what emerges in one country can be a problem in another. We have seen the spread of resistant typhoid fever from Mexico to Los Angeles. Bacteria need neither passports nor visas to travel among the countries. Multiresistant strains now plague us here.

Of importance, the genes for resistance to penicillin and to tetracycline are the same as those first found 10 to 15 years ago in gut organisms. Moreover, the plasmids in Neisseria and Hemophilus are the same. Gene exchanges are occurring all the time.

We are also all becoming carriers of resistant strains bearing transferable resistances. Between 1978 and 1980, my group examined the gut bacteria of ambulatory well people in the Boston area, urban and rural community. We found that three out of every four persons had significant levels of resistant bacteria which could transfer this resistance.

Antibiotics are used not only to treat infections in man, animals, and cultivated plants, but are also used in subtherapeutic levels for growth promotion of animals. I bring this up here because I think it bears on my question of what's happening in our environment. When they're used at any level, they leave behind resistant strains which thrive in the antibiotic-treated environment. To make matters worse, the continued use of a single antibiotic, such as penicillin or tetracycline, can lead to the emergence of bacteria resistant to many different antibiotics.

We studied the effects of subtherapeutic use in chickens on a farm outside of Boston in the mid-1970's. Within 36 to 48 hours after low-level use, essentially all the aerobic fecal bacteria in the chickens were resistant to tetracycline and later to four other antibiotics. Within 3 to 4 months of antibiotic-supplemented feed on the farm, the farmworkers were excreting increased numbers of resistant bacteria despite their not taking antibiotics.

Mr. Chairman, members of this committee, no matter where you use an antibiotic, the consequences of this usage will not—will be seen not only in the individual or group taking the drug, but also in the innocent bystanders—the other bacteria killed by the drug, the people who pick up the resistant strains surviving in the envi-

ronment. Certainly both man and animals are major sources of these resistant strains in our environment.

In 1983, 25 to 30 percent of the 150 million cattle in the United States were being given subtherapeutic growth-promoting amounts of antibiotics. These animals are excreting bacteria resistant not only to the drug in use, but to multiple other antibiotics. Since each cow produces 50 to 90 pounds of fecal material per day, the 30 million cattle in the United States yearly produce 1½ to 2½ billion pounds of feces laden with antibiotic resistant bacteria. The majority of this material is spread as manure on agricultural plots or deposited in landfills or in environmental waters. I could go on with similar statistics for swine. The point is that these, as well as use in hospitals and in community, contribute, I think, in a major way to what is seen in the environment.

The problem is not only with the dispensers, but with the consumers. The attitude that antibiotics cure everything from arthritis to the common cold pervades our culture. Antibiotics are conserved in medicine cabinets to be given out one at a time to treat the sniffling youngster or the aching relative. One mother I heard gave a single antibiotic pill to a whole busload of children because one of them had a cold. There are many other stories in the same light. This mentality and misuse has got to change.

In less developed countries, antibiotics are sold over the counter without prescription. The consequences, I believe, are seen in the emergence of disease-causing bacteria which have inherited the resistance traits even from the nonpathogenic strains.

I hope it is clear from what I presented that the problem of antibiotic misuse and resistance is both local and international, and it should be approached as such. For more than 10 years, this area has been studied by the World Health Organization, culminating in 1981 with the establishment of the Scientific Working Group on Antibiotic Resistance, of which I am a member. And the international organization called the Alliance of the Prudent Use of Antibiotics was established in the same year. Now counting members in 60 countries of the world, these individuals and groups have joined to share in communicating and educating in order to preserve antibiotic effectiveness. Members include basic and medical scientists and others from academia, industry, and the public.

The Fogarty International Center of the National Institutes of Health has been working with a group of 80 international experts from more than 30 countries in all continents examining the state of affairs and research needs relating to antibiotic resistance.

The environmental reservoir of transferable resistance genes continues to threaten human health. As more donor bacteria are created, the chance of transfer to susceptible strains, in particular disease-causing bacteria, rises. The only way to eliminate them is to decrease the selective pressure by using antibiotics in a prudent way. The attitude toward antibiotics must be updated by the dispenser and the user.

Antibiotics are not panaceas, they have a defined activity. But this activity makes even the single user a contributor to resistance in the environment. If antibiotics are used wisely, however, resistant strains will not increase, but rather should decrease, and susceptible ones will return. This is and should be our goal.

Thank you.

Mr. GORE. Thank you very much. That's an excellent statement, and I appreciate it. We'll hold off on questions until the panel has been completed.

[The prepared statement of Dr. Levy follows:]

TUFTS UNIVERSITY
School of Medicine
School of Dental Medicine
School of Veterinary Medicine
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Department of Molecular Biology and Microbiology

December 21, 1984

Dr. Frances Sharples
Subcommittee on Investigations and Oversight
300 New Jersey Avenue, SE
822 House Annex #1
Washington, D.C. 20515

Dear Fran:

In looking over my written report which I sent to you before the hearing, I noted that on page 2 there was a repeat of sentences from page 1. Also, somehow the explanation of transposons was deleted as is obvious from the incoherent sentence at the top of page 6. I have made these corrections and enclose two copies of the corrected version. I would appreciate your seeing that this is the one introduced into the hearings record. Thank you.

I very much enjoyed meeting you and speaking to you.

With all best wishes for the Holiday Season and New Year,

Stuart B. Levy, M.D.
Professor of Medicine
Professor of Molecular Biology
and Microbiology

SBL:WW

enc.

136 Harrison Avenue
Boston, Massachusetts 02111
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Antibiotic resistance a local and international problem

Stuart B. Levy M.D.

Professor of Medicine

Professor of Molecular Biology and Microbiology

Tufts University School of Medicine

Boston. Mass. 02111

Written Statement

For The

Subcommittee On Investigations and Oversight

Committee on Science and Technology

U.S. House of Representatives

December 19, 1984

Bacteria resistant to antibiotics thwart our present day ability to treat even common diseases. Infections of the lung, heart valves, brain, ear, skin, urinary tract, blood stream and other tissues, while not necessarily increasing in frequency, are increasingly caused by bacteria now resistant to antibiotics previously able to effect a cure. These variant strains exist in communities and in hospitals throughout the world. They exist wherever antibiotics have been used, misused and overused. They know no geographic borders. Most importantly, they have become significant components of man's everyday environment. Originally produced by organisms to protect their own limited ecologic niche, antibiotics developed by man now treat large numbers of people and animals and involve vast areas of space. The result, only forty years after clinical use of antibiotics, is widespread resistance and drug ineffectiveness -- a finding scientifically impressive but clinically disturbing. When strains resistant to an antibiotic constitute even a significant minority, then that drug ceases to be the one of choice for the disease. Costly diagnostic tests are required and more expensive, often toxic, new drugs have to be used.

The literature is replete with citations in all languages relating the problems of antibiotic resistance. Pharmaceutical companies are actively devising new ways of circumventing resistance. Hospitals are developing means of controlling antibiotic use in order to curtail resistance and limit costs.

The World Health Organization has wrestled with the problem for many years. In 1981, it formed a Scientific Working Group on Antimicrobial Resistance, of which I am a member, to evaluate and advise on the problem worldwide. The initiative came from a need to understand the problem which was costing valuable lives and resources. Recommendations for antibiotic use and for research were put forth (1).

Somewhat earlier in 1981, at a meeting in the Dominican Republic, a group of medical and basic scientists from 30 countries signed and released a "Statement regarding worldwide antibiotic misuse" which outlined the consequences to human health and health dollars of resistance. The group stated what was to some the obvious: antibiotics were being misused (2). But to a large number of people worldwide this was news. The response which followed led to the formation of an international organization dedicated to educating various groups about antibiotics, their use and resistance, and to forming a network of individuals and groups interested in these valuable natural resources. Antibiotics are a special group of drugs since their activity affects not only the bacteria and the patient undergoing treatment but also the environment. The Alliance for the Prudent Use of Antibiotics comprises about 400 dues-paying members from almost 60 countries and corresponds with many others worldwide. It is a nonpolitical, tax-exempt educational organization whose aims are to preserve through education, research and communication the effectiveness of antibiotics. Its quarterly Newsletter carries articles relevant to understanding antibiotic use and resistance worldwide. APUA's growing recognition and increasing membership (without a formal appeal) has demonstrated the need for such an organization and the existence of individuals eager to address the problem.

Most recently, the Fogarty International Center of the National Institutes of Health is working with individuals and groups worldwide in developing an international conference set for early 1986 as a forum to consider the state of affairs and research needs relating to antibiotic use and resistance worldwide. Other international colloquia and conferences discuss the problem regularly in all major continents of the world.

A Trends in Resistance

Sulphonamides were magic to medicine when they were introduced into clinical practice in the 1930s. They were surpassed only by the discovery and use of penicillin in the 1940s. The appearance of penicillin resistant Staphylococcus aureus soon after man began using this drug demonstrated that the gene for the destruction of penicillin, itself a naturally occurring substance, was also present in nature. By the 1960s, only 20 years later, clinicians began to see a significant erosion in the effectiveness of these drugs in the treatment of human and animal diseases. And this trend has continued to increase since then. While we can accept that certain numbers of resistant bacteria would normally have appeared following the introduction of antibiotics, what concerns many of us is that resistance continues to increase entering new bacterial species and new environments previously virgin. Of importance, the genes and mechanisms for resistance in the newer strains appear to have been inherited or derived from those found earlier in other species, strongly suggesting that they have been picked up, propagated and maintained in the new species under the continued selection of antibiotics. Today we see penicillin-resistant bacteria which cause typhoid fever, dysentery, gonorrhea, meningitis, septicemia, urinary tract infection, pneumonias and other diseases.

Another example shows how an effective more recent drug can be quickly disarmed because indiscriminate use has continued. The combination of trimethoprim and sulfamethoxazole, or co-trimoxizole, is a novel use of a fixed combination of two chemicals which inhibit the production of an important nutrient needed by bacteria. The combination was introduced in the early 70s as a means to circumvent rapid emergence of resistance since the two

drugs act at different sites in the synthesis of this substance. Within only several years, however, the use of this drug in England was followed by resistant isolates in London hospitals. In a 1977 editorial in the New England Journal of Medicine, I warned against the overuse of this effective combination in simple urinary tract infection (3). Still I witnessed use of this drug rather than older, still useful drugs in treating common infections. In 1979, six years after its introdution here, resistance to co-trimoxazole had not yet been a problem (4). But, in 1982 came the report of two leukemic patients in Los Angeles who died of a co-trimoxazole resistant E. coli showing that the use of the effective drug combination could no longer be guaranteed. Multiply resistant, co-trimoxazole resistant strains of gram negative bacteria appeared in the feces of U.S. travelers in Mexico after taking the drug for prophylaxis of diarrhea. The message -- continued use would likely set them up for more severe infection with resistant pathogenic strains. Of importance neighboring Mexico was already reporting resistant bacteria, both nonpathogenic and pathogenic types, bearing transferable resistances so that these strains could receive and donate their resistance among different types of bacteria. The increase in co-trimoxazole resistant gut bacteria in Mexico was found to correlate with an 8-fold increase in co-trimoxazole usage (much over-the-counter) in Mexico from 1977-1980. It should not be surprising, therefore, that in a recent report of transplant patients 39% of them had co-trimoxazole resistant gut bacteria at more than 10^6 per gram of feces and of these 8% developed blood infection of which 75% were resistant to this drug combination (5).

B. Factors affecting antibiotic resistance

Human and microbial factors affect the emergence and spread of antibiotic resistance.

1. Antibiotic Use

The use of antibiotics at subtherapeutic or therapeutic levels in any environment will eliminate susceptible organisms and leave the resistant ones to survive. Antibiotics also alter the microenvironment giving advantage to resistant strains which can colonize those antibiotic-devastated areas where competition from other strains is eliminated. It is like inadvertently killing off all grass in attempting to kill crab grass, but resistant survivors of the latter soon take over the lawn. Use of a narrow spectrum drug which affects only the organism of interest would help not only in maintaining the competitive susceptible flora but also prevent the emergence of resistance in other organisms who are, so to speak, innocent bystanders. More importantly, in both animals and in man, we and others have found that the chronic use of a single antibiotic, especially tetracycline and penicillin, will lead to the emergence of multiply resistant bacteria, that is bacteria resistant not only to the drug in use but to other drugs which are structurally unrelated (6,7).

2. The genetics of resistance - an important microbial factor

Resistance determinants reside on intracellular DNA molecules called plasmids that can exchange among bacteria of very different types. Very often the gene for resistance is on an even smaller unit of DNA, called a transposon, which can "jump" from one DNA vehicle to another. By

jumping onto the chromosome they can be transferred into bacteria where the plasmid itself may be lost. This explains the rapid appearance of resistance determinants in a wide array of bacteria especially in environments where the resistant determinants are selected by antibiotic use. Anerobes can exchange with aerobes and resistance genes can insert into plasmids stable in one host and not another.

3. The "environmental pool of resistance"

Once selected by an antibiotic, a resistant organism joins the environmental pool. Each time an antibiotic is introduced, it provides advantage to resistant strains which increase in number. They can spread their resistance genes to neighboring susceptible strains or combine resistance traits with those on other plasmids to create the multiply resistant strain. Who contributes to the pool? All environments of antibiotic use contribute to the pool unless the bacterial components are somehow destroyed. Thus, antibiotic use in hospitals, homes, farms etc. select resistant bacteria and increase their numbers in the environment. An important contributor is fecal load. Each ingestor by killing off susceptible gut flora allows colonization with resistant types. Each mass of feces carries with it a large number (10^6-10^8/gram) of aerobic bacteria which are resistant in an antibiotic being ingested.

In the U.S., about 200 million antibiotic prescriptions are written, less than the number of inhabitants (8). The doses are for therapy and for definite periods of time. Human fecal mass in the U.S. is generally removed by treatment plants which may eventually dessicate (which kills all) or treats which may reduce numbers by 10^{-3}-10^{-4} (9).

Large farm animals are more prodicious contributors to bacterial environmental mass. About 115 million cattle were estimated in the U.S. in 1983 (10) of which about 30% were being treated with subtherapeutic amounts of antibiotics. Given 50-90 poinds of feces/day, (11) the amount of bacteria excreted amounts to 400 times that produced by man. Pigs produce about ten-fold less fecal material (2-5 pounds/day) with about 43 million of them on antibiotics throughout most of their lives (10,11).

Since the majority of animals waste is spread as manure or slurry onto agricultural soils or used to fill in dump sites or even placed in waters, most of the resistant bacteria so produced enter directly into the environment. Thus if one accepts a common environment for man, animals and agriculture, then one sees animals as a major source of resistant strains of enteric bacteria in the environment.

4. Spread among individuals and animals in the environment

Spread of bacteria among people, among animals, and among people, animals and the environment is common to all bacteria, resistant or susceptible. Animal to human spread has been reported repeatedly, most recently in a review of salmonellosis by the Centers for Disease Control (12). The reverse may also occur. We recently demonstrated that wild baboons in Kenya. feeding on human refuse, had antibiotic resistant gut flora which significantly contrasted with their siblings who lived in the wild without human contact and who maintained a uniquely susceptible gut flora. In a recent study of the bacterial flora of ambulatory persons living in Boston we found that 3/4 had gut flora resistant to at least one antibiotic at a level of more than 10%. A significant number were resistant to more than one antibiotic (13).

5. Food

Visitors to foreign countries may require 48 hours in that country before their bacterial flora is altered. A steady diet of new bacteria may eventually lead to changes in the gut flora with new organisms now colonizing. But the time between ingestion and colonization may be influenced by antibiotics. The taking of a single antibiotic will cause an alteration of the bacterial flora so that largely those which are resistant to that antibiotic or that antibiotic combination will survive. If the ingestor takes an antibiotic the chance of picking up a resistant infective bacteria would increase. This is one reason to avoid the prophylactic use of antibiotics for dysentery especially in countries where resistant pathogens are prevalent.

It is becoming increasingly more evident that resistant bacteria are contaminants of common fruits and vegetables. In a recent study we performed examining raw fruits and vegetables in the Boston area, we detected enteric bacteria including E. coli and pseudomonas in addition to commonly found soil organisms (which are non pathogenic) at levels which could potentially colonize the human gut (14). It is for this reason that at our hospital and other hospitals a "cooked food only" diet is advised for patients undergoing chemotherapy for cancer because their compromised condition increases their chances of contracting illness not only by the occasional pathogen but also by resistant variants of non-pathogenic gut bacteria which can cause disease in this high risk group.

C. Emergence of resistance in the community

While resistance was initially a problem in large urban hospitals, it has

now moved into communities, a trend which warrants particular attention.

To illustrate the problem I shall describe some of the major organisms causing human diseases which have recently appeared resistant to effective treatment. I shall not discuss the enteric bacteria, e.g. Salmonella, Shigella since their resistance has been known for some time.

1. Staphylococci

Staphylococcus aureus was the organism which revealed to Alexander Fleming the potential use of penicillin in the treatment of bacterial diseases. However, resistance in the species did not lag far behind usage of this antibiotic. Within a four year period after introduction into a London hospital, resistant strains of Staphylococcus were at 59%. During these early years, the community was spared and resistance appeared to be the result of heavy use of penicillin in hospitals. Today, 40 years later, the situation is very different. Only about 10-15% of Staphylococcus aureus infections even in the communities, respond to penicillin. Modified forms of penicillin, such as methicillin, resistant to the destructive bacterial enzyme, were developed to treat these diseases. Introduced in 1959, resistance to methicillin appeared two years later in Europe and a decade later in the United States. In fact, Staphylococcus aureus resistant to methicillin and other different antibiotics has become a major problem in many centers. In Melbourne, Australia the availability of only a single drug, vancomycin, effective against a multiply resistant staphylococcus infection in their hospitals led to the establishment of a committee to improve antibiotic usage and to curb the resistant infection. Their Antibiotic Guidelines was established to do just that (15).

In many U.S. studies, methicillin-resistant staphylococci in hospitals has

been linked to their initial appearance in the community. Once introduced they spread among patients and personnel. In one study from Charlottesville, Virginia a single index case of methicillin-resistant Staphylococcus aureus introduced into a community unit hospital resulted 6 months later in 30 additional patients, 22 of whom were epidemically linked to the initial index case (16). Sixteen of the 31 cases were infected and 6 had bacteremias.

Similar links with the community were stressed in a series of papers in the Annals of Internal Medicine in 1982. The Henry Ford Hospital in Detroit, Michigan reported 165 patients with 183 infections caused by community-acquired methicillin-resistant Staphylococcus aureus (17). The proportion of community-acquired infections rose from 3% in March of 1980 to 38% in September of 1981.

Resistance now plagues clinicians and patients in the common "nonpathogenic" staphylococcus epidermidis which infects prosthetic valves and other artificial tissues. An estimated 25% of the cases of endocarditis are now caused by Staphylococcus epidermidis with mortality as high as 63-74% (18). These organisms, like their relatives the Staphylococcus aureus are resistant to the penicillins, including the methicillins, cephalosporins and to many other useful antibiotics.

2. Streptococci

Streptococci can transfer resistance genes not only among their own genera but also among other coccal and rod shaped species including staphylococci, Listeria and Lactobacillus. Resistance genes from this organism can be expressed even in gram negative bacteria. Among the streptococci the beta hemolytic types cause considerable harm to man, e.g. rheumatic heart disease,

scarlet fever and "strep throat." Recently it has been shown that different groups of beta hemolytic streptococci contain transferable multiple resistances, including that to erythromycin, tetracycline, chloramphenicol, kanamycin, and streptomycin. In a study in France, 38% of multiply resistant beta-hemolytic streptococci had transferable resistances (19). The mainstay of treatment is still penicillin, however, relatively resistant strains have been reported in the U.S. as they have in other parts of the world. Streptococcus viridans, commonly associated with subacute bacterial endocarditis, has also emerged with variants resistant to penicillin (20). Since both of these organisms are often resistant to tetracycline, this inexpensive second choice may also be ineffective.

Perhaps the most worrisome of the recent findings of resistance in streptococci relates to the enterococcus, an organism isolated from urinary tract infections, wound infections and associated with certain septicemias and abcesses. High level transferable resistance to the effective drug gentamicin is accompanied by high level resistance to other effective aminoglycosides. B. Murray and associates in Houston, Texas have recently demonstrated a transferable resistance to penicillin which is secondary to the production of an enzyme which breaks down penicillin (21). The ability of this organism to transfer resistances to different types of streptococci raises tremendous concern that these newly emerging resistances will soon move into clinically important streptococci, such as the Group A strains, making penicillin and penicillin derivatives ineffective in the treatment of common and, up to now, controllable infections.

3. Pneumococcus

Pneumococcal pneumonia was the scourge of the pre-antibiotic era but was greatly rebuked by the sulfonamides in the 1930s and penicillin during the 1940s. But beginning in the 1960s, isolated reports of penicillin resistant pneumococcus causing treatment failures appeared in different parts of the world. In South Africa in 1977 a pneumococcus resistant to the penicillin-like antibiotics, erythromycin, clindomycin, tetracycline and chloramphenicol was introduced from the community into a hospital. From there it spread among patients and personnel (22). Pneumococci can transfer these genes to other streptococci and the same resistance genes are found in other streptococci and in Staphylococcus aureus. In an editorial in 1978 Dr. Maxwell Findland stated "we can no longer be complacent about treating pneumococcal pneumonia with small doses of penicillin nor can we be satisfied without testing for the susceptibility of the cultured organisms" (23).

A highly penicillin-resistant strain of pneumococcus was found in Minnesota in 1977. It was difficult to treat an 11 month old child in Colorado from whom a penicillin, chloramphenicol, tetracycline resistant pneumococcus was isolated from the cerebrospinal fluid. Today in the United States patients suffer from pneumococcal infections resistant to penicillin, chloramphenicol, tetracycline and multiple other antibiotics.

4. Neisseria

Neisseria gonorrhea is the organism associated with the venereal disease gonorrhea. High level resistance to penicillin first appeared in this organism in 1976. Since then resistance to tetracycline, and to other effective drugs previously used to treat this organism, is now found in Neisseria throughout the world and multiply resistant strains are rapidly

appearing.

Penicillin resistant Neisseria were imported into the U.S. from Southeast Asia where resistance frequency in this organism can be as high as 60%, e.g. Korea and Thailand. While in 1976, 19 states reported the isolation of these resistant organisms, by 1982-1983 all of the United States had reported as few as 2 and as many as 1250 cases of penicillin-resistant gonorrhea. How the gene entered Neisseria is unknown but can be speculated from what we know about resistance transfer. The origin of the antibiotic inactivating gene appears to be the enteric bacteria. It is the same originally found in penicillin-resistant E.coli 10-15 years before (24).

A different form of penicillin resistance is now emerging in the United States which is not imported, but is occurring locally -- the appearance of penicillin-resistant strains which do not destroy the enzyme but impede its entry or site of action in the cell. Initially described in North Carolina, there are now cases of this form of resistant bacteria reported in Tennessee, New Mexico, Oregon and thirteen other states (25). These strains are not only resistant to penicillin but also to the second drug of choice in this disease, tetracycline.

Gonorrhea is a disease generally treated in the community. While it is a disease limited to man, the organisms, like all, share the common environment. In the United States, resistance in a single type of Neisseria gonorrhea has now spread to other different types. Like other bacteria Neisseria can transfer resistances among other types of Neisseria and even into E.coli.

5. Hemophilus influenzae

An estimated 15,000 to 20,000 cases of systemic H.influenzae infection

appear in the U.S. yearly, mostly in children less than 5 years. The bacteria cause ear infections and meningitis that can be debilitating and lethal. In adults, severe pneumonias can arise. The course of these diseases was changed dramatically with the introduction of the penicillin derivative ampicillin. But ampicillin resistance appeared in the mid 1970's. Of importance, resistance to this organism was first reported in a community outside of Bethesda, Maryland (26) and was subsequently found in other communities inside and outside the United States. Today, as presented in the enclosed table (Table 1), resistance to this and other antibiotics, while reported initially in many different countries including the United States, (35-40% in some parts of the U.S.) has spread to all parts of the world.

In a 1984 review from the departments of pediatrics from Seattle, San Francisco and Athens, Greece the authors warned "clinicians need to be aware of the recent emergence of multiply resistant isolates of H. influenzae type b. Because resistance in this organism has commonly been due to the acquisition of R plasmids, more such strains will probably be encountered in the future" (27).

Like Hemophilis influenzae the less pathogenic H. parainfluenzae, a normal constituent of the throat flora, can carry and exchange resistances with the more pathogenic types. The frequency of penicillin resistance may be 2-3 times higher than in H. influenzae. Resistance is also linked to penicillinase production and the gene is strikingly similar if not identical to that which was originally found in Neisseria and in the enteric bacteria many years before. Of interest, emphasizing the promiscious exchange of resistance genes, was the finding that plasmids in H. influenzae and in N. gonorrhea are similar if not exactly the same (28).

Another clinically important Hemophilus is H.ducreyi which causes the

venereal disease, chancroid. Its resistance patterns include sulfonamides, tetracycline, and ampicillin -- all transferable (29). Virtually all clinical isolates of Hemophilus ducreyi were found resistant to tetracycline in Kenya; clinical isolates in the U.S. have also shown high level resistance in some areas of the country. 96% of 103 strains of Hemophilus ducreyi isolated in South Africa were resistant to penicillins via a penicillinase and most of these showed concurrent resistance to tetracycline and sulfonamides. While these findings indicate that use of these drugs to treat Hemophilus infections is becoming limited, it is not yet time for despair since other drugs including co-trimoxazole and the new cephalosporins are still active. However, it is important that caution be exercised since resistance to even these drugs has been reported in these organisms.

D. Factors leading to decreased resistance

1. Removal of antibiotics

Studies have shown that the removal of the antibiotic will eventually lead to the return of an acceptable susceptible flora. We have demonstrated this among chickens and humans working on a farm; others have demonstrated this in a hospital setting. But the change is much slower than the rapid appearance of resistance. On the farm it took months before the chicken gut flora lost resistance to tetracycline despite a new environment (30). This is presumably because the addition of a small resistance gene to an organism with much more DNA is not an important energy drain. Moreover, these bacteria maintain their plasmids without selection because the plasmid itself may be critical to the

survival of the strain in this environment.

While we know that antibiotic selection is a major force ecologically we know little about the other forces which cause organisms to remain in an environment. Research into this area is very much needed. Certainly, epidemic infections are not caused by antibiotic resistance although they will be more difficult to contain and consequently cause more illness than if resistance were not a present.

In an intensive care nursery in Gainsville, Florida kanamycin was removed from use because of a resistant nosocomial infection caused by plasmid-mediated resistance. A striking decrease in the resistance levels over the next fifteen months was noted. The substituted drug, gentamicin, however, did lead to an increase in the numbers of bacteria resistant to this drug but no clinical infections were observed (31).

2. Diluting the environmental load

In our study of chickens, an increase in loss of resistant bacteria was effected by introducing susceptible organisms into the environment either in untreated chickens, or a changed environment (30). This finding proved again that resistant bacteria have no advantage or disadvantage in the absence of antibiotics. Competition with numbers of other bacteria will determine the net size of the resistance pool.

V. Summary

The levels of spread of bacteria resistance is multifold. First is the bacterial spread among man, animals, and the environment. Then there is the spread of plasmids among bacteria -- a process now known to involve different kinds of bacteria. Finally there is the spread of transposons between DNA plasmid vectors of many different kinds and in many different species.

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TABLE 1

FIRST APPEARANCE OF RESISTANCE IN HAEMOPHILUS SP.

Year	Resistance*	Country
1972	Cm	U.S.A.
1973	Tc	Australia
1973	Ap	U.S.A.
1975	Km	France
1976	Cm,Tc	France
1978	Ap,Cm,Tc	Canada
1979-80	Ap,Cm	U.S.A.;Thailand
1981	Ap,Cm,Tc,Su+Tm	England

* Ap=ampicillin;Cm=chloramphenicol; Km= kanamycin; Su+Tm= co-trimoxazole; Tc=tetracycline

Mr. GORE. Dr. Jim Hughes is next, Director of the Hospital Infections Program with the Centers for Disease Control. Dr. Hughes, welcome and please proceed.

[The biographical sketch of Dr. Hughes follows:]

James M. Hughes, M.D.
Director, Hospital Infections Program
Center for Infectious Diseases
Centers for Disease Control
Public Health Service
U. S. Department of Health and Human Services

Dr. Hughes received his M.D. degree from Stanford University School of Medicine and completed 3 years of training in internal medicine at the University of Washington in Seattle. He joined the Centers for Disease Control (CDC) as an Epidemic Intelligence Service (EIS) officer and worked for 2 years on the epidemiology of enteric diseases. He subsequently completed a 2-year infectious diseases fellowship at the University of Virginia and returned to CDC to continue his work on the epidemiology and control of enteric diseases in the United States and abroad. He has served as a consultant in this area to the U.S. Agency for International Development and the World Health Organization.

Dr. Hughes joined the Hospital Infections Program in July 1981. He has directed the National Nosocomial Infection Study, a collaborative group of hospitals reporting nosocomial infection data to CDC, since that time. He has been Director of the Hospital Infections Program since July 1983.

Dr. Hughes has completed the CDC Preventive Medicine Residency Training Program. He is board certified in internal medicine, infectious diseases, and preventive medicine and is a Fellow of the American College of Physicians and the Infectious Diseases Society of America.

Dr. HUGHES. Thank you.

Mr. Chairman and members of the—of the subcommittee, I am James M. Hughes, M.D., Director of the Hospital Infections Program in the Center for Infectious Diseases at the Centers for Disease Control, U.S. Public Health Service. I appreciate the opportunity to testify before the subcommittee today. I will summarize some of the data on the frequency of resistance of certain hospital-acquired bacteria to selected antibiotics that were reported to CDC during the past few years by hospitals participating in a voluntary nationwide surveillance program.

A hospital-acquired or nosocomial infection is an infection occurring during hospitalization that was not present or incubating at the time the patient was admitted to the hospital. Some infections with onset shortly after the patient is discharged from the hospital may also be nosocomial. Each year, approximately 2 million nosocomial infections occur in patients in acute-care hospitals in this country. These infections result in prolonged hospital stays, increases in patient care costs, and occasionally in death.

The magnitude of the public health problem of nosocomial infections in this country began to be appreciated during the 1950's. During the past 25 years, substantial progress has been made in organizing and implementing infection surveillance and control programs in hospitals throughout the country. Research has shown that approximately one-third of those infections that would occur in the absence of effective hospital surveillance and control programs could be prevented by well organized optimal programs. One of the many problems with which such programs must deal is bacteria that are resistant to commonly used antibiotics and that may be transmitted from patient to patient in the hospital.

Since 1970, the Centers for Disease Control has conducted nationwide surveillance of nosocomial infections through hospitals participating in the National Nosocomial Infections Study, which I will refer to as NNIS; 75 hospitals which are geographically representative of all U.S. acute-care hospitals voluntarily participate in NNIS. These hospitals conduct continuous surveillance of their patients using uniform definitions of nosocomial infections and report data on their infected patients to CDC. We provide participating hospitals with monthly summaries of their own nosocomial infection rates and with semiannual summaries of the frequency of resistance of their own nosocomial pathogens to selected antibiotics. At CDC, we use the data from all participating hospitals to monitor nationwide trends in nosocomial infection rates and in antibiotic resistance of important nosocomial pathogens.

We group NNIS hospitals into three categories for the purpose of analysis. These categories are: First, large medical-school-affiliated hospitals with more than 500 beds; second, small medical-school-affiliated hospitals with 500 or fewer beds; and third, all hospitals not affiliated with medical schools. Nosocomial infection rates are generally highest in the large affiliated hospitals, intermediate in the small affiliated hospitals, and lowest in the nonaffiliated hospitals. These differences primarily reflect differences in average level of patient risk for nosocomial infection between these categories of hospitals.

Let us now briefly consider some trends in the frequency of resistance of certain important bacterial pathogens that cause nosocomial infections to specific antibiotics. I will comment on methicillin resistance of Staphylococcus aureus and aminoglycoside resistance and third-generation cephalosporin resistance of gram-negative bacteria.

Staph aureus is a common nosocomial pathogen that gained notoriety during the 1950's as a cause of many outbreaks in nurseries, which led to recognition of the importance of the nosocomial infection problem. Shortly after the antibiotic methicillin was introduced into clinical use in 1959, strains of Staph aureus resistant to methicillin began to appear in European hospitals. However, methicillin-resistant strains were rarely encountered in hospitals in this country until the mid-1970's. Since that time, these organisms have been reported to cause both nosocomial infection outbreaks and endemic infections in a number of hospitals throughout the country.

NNIS data indicate that the frequency with which hospitals isolate methicillin-resistant strains has increased steadily since 1975. Analysis of these data for the past 5 years, shown in figure 1, which is attached, reveals that resistance of Staph aureus nosocomial infection isolates to methicillin has increased steadily. More detailed analysis of these NNIS data, shown in figure 2 which is also attached, indicates that the increase is occurring almost exclusively in one of the three categories of hospitals—specifically in the large medical-school-affiliated hospitals with more than 500 beds, and not in the smaller affiliated or the nonaffiliated hospitals. We are not certain why this is so. However, we think it may be due, at least in part, to the large number of seriously ill patients in critical care units in these hospitals, the difficulty in eradicating resistant strains from these units once they are introduced, and possibly also to different patterns of antibiotic use in these hospitals.

As a group, aerobic gram-negative bacteria cause over half of all nosocomial infections. Members of the family Enterobacteriaceae and species of the Pseudomonas genus are responsible for the—the vast majority of these infections. The aminoglycoside antibiotics, gentamicin and tobramycin, which were introduced into clinical use in the mid-1960's and mid-1970's, respectively, have been used as the agents of choice for treatment of infections due to those organisms that were resistant to older, less toxic drugs.

NNIS data indicate that resistance to these drugs among members of the enter—Enterobacteriaceae family increased from 1975 through 1978, following which there has been little change. When these data are examined more closely, the frequency of resistance in organisms causing infections in patients on the adult medical and surgical services has remained about the same since 1978. However, on the pediatric and newborn services, the frequency of resistance has continued to increase. The frequency of resistance of Pseudomonas species has continued to increase throughout this period. As was the case with methicillin-resistant Staph aureus strains, the frequency of resistance of both groups of gram-negative bacteria to these aminoglycosides is substantially greater in the large medical school-affiliated hospitals than in the smaller affili-

ated hospitals and the nonaffiliated hospitals, probably for the same reasons mentioned previously.

During 1981, the first two of the new third-generation cephalosporin antibiotics, cefotaxime and moxalactam, were introduced into clinical use in this country. These drugs are intended primarily for the treatment of infections caused by members of the Enterobacteriaceae family that are resistant to older drugs. These drugs also provide a less toxic alternative to the previously mentioned aminoglycoside antibiotics.

NNIS has monitored the frequency of resistance of gram-negative bacteria to these agents for nearly 3 years, but the frequency of resistance to these agents does not yet appear to be increasing. In contrast to the trends with methicillin-resistant Staph aureus and aminoglycoside-resistant gram-negative bacteria, the frequency of resistance to these agents is similar in both medical school-affiliated and nonaffiliated hospitals. Some regional differences in the frequency of resistance to these agents have been noted, however.

Several factors should be considered when interpreting these data. First, NNIS hospitals are a voluntary rather than a random sample of all U.S. hospitals. However, NNIS members are reasonably representative of nonmedical school-affiliated hospitals with more than 200 beds, all small affiliated hospitals, and all large affiliated hospitals. Second, resistant strains of bacteria are not routinely collected from these hospitals for confirmation of resistance at CDC. Hospital laboratories are quite accurate in their determination of resistance of gram-negative bacteria to the aminoglycosides and third-generation cephalosporins. In the past, however, some laboratories may have had problems in recognizing methicillin-resistant strains of Staph aureus.

In closing, I have described the nationwide system for the surveillance of nosocomial infections and have reviewed trends in the frequency of methicillin resistance in Staph aureus and aminoglycoside and third-generation cephalosporin resistance in gram-negative bacteria. Methicillin resistance in Staph aureus is continuing to increase in large medical school-affiliated hospitals. Aminoglycoside resistance in the Enterobacteriaceae family of gram-negative bacteria has plateaued, although closer examination of the data suggests that resistance is continuing to increase on pediatric and newborn services. The frequency of resistance of Pseudomonas species has continued to increase. Finally, there are as yet no clear trends in the frequency of resistance of gram-negative bacteria to the new third-generation cephalosporins, although some differences in frequency of resistance in different geographic regions are apparent.

We cannot comment at this time about the relationship of antibiotic use in the different hospitals participating in NNIS to the pattern of resistance observed because we do not have data on antibiotic use in these hospitals. We are currently developing a mechanism to initiate surveillance of antibiotic use in these institutions in an effort to assess the relationship of use to reported patterns of resistance.

Mr. Chairman, this concludes my formal testimony. I would be happy to answer any questions you or other members of the subcommittee may have.

Mr. GORE. Great. Thank you very much.

[The prepared statement of Dr. Hughes follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
Atlanta, Georgia 30333

B/

STATEMENT OF

JAMES M. HUGHES, M.D.

DIRECTOR, HOSPITAL INFECTIONS PROGRAM

CENTER FOR INFECTIOUS DISEASES

CENTERS FOR DISEASE CONTROL

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

COMMITTEE ON SCIENCE AND TECHNOLOGY

U.S. HOUSE OF REPRESENTATIVES

DECEMBER 19, 1984

Mr. Chairman and Members of the Subcommittee:

I am James M. Hughes, M.D., Director of the Hospital Infections Program in the Center for Infectious Diseases at the Centers for Disease Control, U.S. Public Health Service. I appreciate the opportunity to testify before the Subcommittee today. I will summarize some of the data on the frequency of resistance of certain hospital-acquired bacteria to selected antibiotics that were reported to CDC during the past few years by hospitals participating in a voluntary nationwide surveillance program.

A hospital-acquired or nosocomial infection is an infection occurring during hospitalization that was not present or incubating at the time the patient was admitted to the hospital. Some infections with onset shortly after the patient is discharged from the hospital may also be nosocomial. Each year, approximately 2 million nosocomial infections occur in patients in acute-care hospitals in this country. These infections result in prolonged hospital stays, increases in patient care costs, and occasionally in death. The magnitude of the public health problem of nosocomial infections in this country began to be appreciated during the 1950's. During the past 25 years, substantial progress has been made in organizing and implementing infection surveillance and control programs in hospitals throughout the country. Research has shown that approximately 1/3 of those infections that would occur in the absence of effective hospital surveillance and control programs could be prevented by well organized, optimal programs. One of the many problems with which such programs must deal is bacteria that are resistant to commonly used antibiotics and that may be transmitted from patient to patient in the hospital.

Since 1970, the Centers for Disease Control (CDC) has conducted nationwide surveillance of nosocomial infections through hospitals participating in the National Nosocomial Infections Study (NNIS). Seventy-five hospitals which are geographically representative of all U.S. acute-care hospitals voluntarily participate in NNIS. These hospitals conduct continuous surveillance of their patients using uniform definitions of nosocomial infections and report data on their infected patients to CDC. We provide participating hospitals with monthly summaries of their own nosocomial infection rates and with semi-annual summaries of the frequency of resistance of their own nosocomial pathogens to selected antibiotics. At CDC, we use the data from all participating hospitals to monitor nationwide trends in nosocomial infection rates and in antibiotic resistance of important nosocomial pathogens.

We group NNIS hospitals into three categories for the purpose of analysis. These categories are 1) large medical school-affiliated hospitals with more than 500 beds, 2) small medical school-affiliated hospitals with 500 or fewer beds, and 3) all hospitals not affiliated with medical schools. Nosocomial infection rates are generally highest in the large affiliated hospitals, intermediate in the small affiliated hospitals, and lowest in the non-affiliated hospitals. These differences primarily reflect differences in average level of patient risk for nosocomial infection between these categories of hospitals.

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Let us now briefly consider some trends in the frequency of resistance of certain important bacterial pathogens that cause nosocomial infections to specific antibiotics. I will comment on methicillin resistance of Staphylococcus aureus and aminoglycoside resistance and third-generation cephalosporin resistance of gram-negative bacteria.

S. aureus is a common nosocomial pathogen that gained notoriety during the 1950's as a cause of many outbreaks in nurseries, which led to recognition of the importance of the nosocomial infection problem. Shortly after the antibiotic methicillin was introduced into clinical use in 1959, strains of S. aureus resistant to methicillin began to appear in European hospitals. However, methicillin-resistant strains were rarely encountered in hospitals in this country until the mid-1970's. Since that time, these organisms have been reported to cause both nosocomial infection outbreaks and endemic infections in a number of hospitals throughout the country. NNIS data indicate that the frequency with which hospitals isolate methicillin-resistant strains has increased steadily since 1975. Analysis of these data for the past five years, shown in Figure 1 (attached), reveals that resistance of S. aureus nosocomial infection isolates to methicillin has increased steadily. More detailed analysis of these NNIS data, shown in Figure 2 (attached), indicates that the increase is occurring almost exclusively in one of the three categories of hospitals--specifically in the large medical school-affiliated hospitals with more than 500 beds--and not in the smaller affiliated or non-affiliated hospitals. We are not certain why this is so. However, we think it may be due at least in part to the large number of seriously ill

patients in critical care units in these hospitals, the difficulty in eradicating resistant strains from these units once they are introduced, and possibly also to different patterns of antibiotic use in these hospitals.

As a group, aerobic gram-negative bacteria cause over half of all nosocomial infections. Members of the family Enterobacteriaceae and species of the Pseudomonas genus are responsible for the vast majority of these infections. The aminoglycoside antibiotics gentamicin and tobramycin, which were introduced into clinical use in the mid-1960's and mid-1970's, respectively, have been used as the agents of choice for treatment of infections due to those organisms that were resistant to older, less toxic drugs. NNIS data indicate that resistance to these drugs among members of the Enterobacteriaceae family increased from 1975 through 1978, following which there has been little change. When these data are examined more closely, the frequency of resistance in organisms causing infections in patients on the adult medical and surgical services has remained about the same since 1978. However, on the pediatric and newborn services, the frequency of resistance has continued to increase. The frequency of resistance of Pseudomonas spp. has continued to increase throughtout this period. As was the case with methicillin-resistant S. aureus strains, the frequency of resistance of both groups of gram-negative bacteria to these aminoglycosides is substantially greater in the large medical school-affiliated hospitals than in the smaller affiliated hospitals and the non-affiliated hospitals, probably for the same reasons mentioned previously.

During 1981, the first two of the new third-generation cephalosporin antibiotics, cefotaxime and moxalactam, were introduced into clinical use in this country. These drugs are intended primarily for the treatment of infections caused by members of the Enterobacteriaceae family that are resistant to older drugs. These drugs also provide a less toxic alternative to the previously mentioned aminoglycoside antibiotics. NNIS has monitored the frequency of resistance of gram-negative bacteria to these agents for nearly three years, but the frequency of resistance to these agents does not yet appear to be increasing. In contrast to the trends with methicillin-resistant S. aureus and aminoglycoside-resistant gram-negative bacteria, the frequency of resistance to these agents is similar in both teaching and non-teaching hospitals. Some regional differences in the frequency of resistance to these agents have been noted, however.

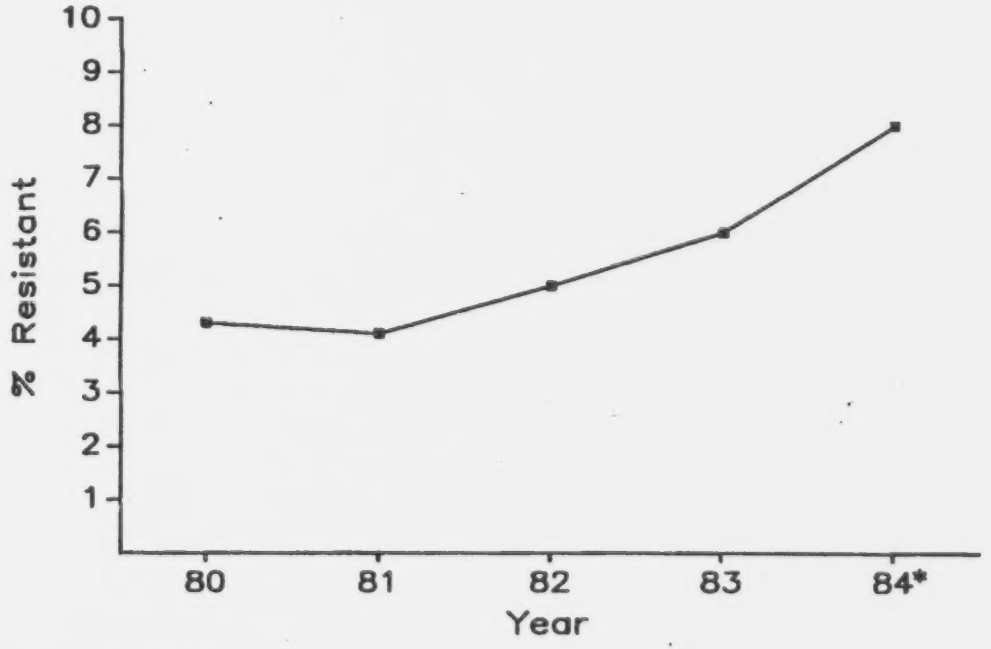
Several factors should be considered when interpreting these data. First, NNIS hospitals are a voluntary rather than a random sample of all U.S. hospitals. However, NNIS members are reasonably representative of non-medical school-affiliated hospitals with more than 200 beds, all small affiliated hospitals, and all large affiliated hospitals. Second, resistant strains of bacteria are not routinely collected from these hospitals for confirmation of resistance at CDC. Hospital laboratories are quite accurate in their determination of resistance of gram-negative bacteria to the aminoglycosides and third-generation cephalosporins. In the past, however, some laboratories may have had problems in recognizing methicillin-resistant strains of S. aureus.

In closing, I have described the nationwide system for the surveillance of nosocomial infections and have reviewed trends in the frequency of methicillin resistance in S. aureus and aminoglycoside and third-generation cephalosporin resistance in gram-negative bacteria. Methicillin resistance in S. aureus is continuing to increase in large medical school-affiliated hospitals. Aminoglycoside resistance in the Enterobacteriaceae family of gram-negative bacteria has plateaued, although closer examination of the data suggests that resistance is continuing to increase on pediatric and newborn services. The frequency of resistance of Pseudomonas spp. has continued to increase. Finally, there are as yet no clear trends in the frequency of resistance of gram-negative bacteria to the new third-generation cephalosporins, although some differences in frequency of resistance in different geographic regions are apparent.

We cannot comment at this time about the relationship of antibiotic use in the different hospitals participating in NNIS to the pattern of resistance observed because we do not have data on antibiotic use in these hospitals. We are currently developing a mechanism to initiate surveillance of antibiotic use in these institutions in an effort to assess the relationship of use to reported patterns of resistance.

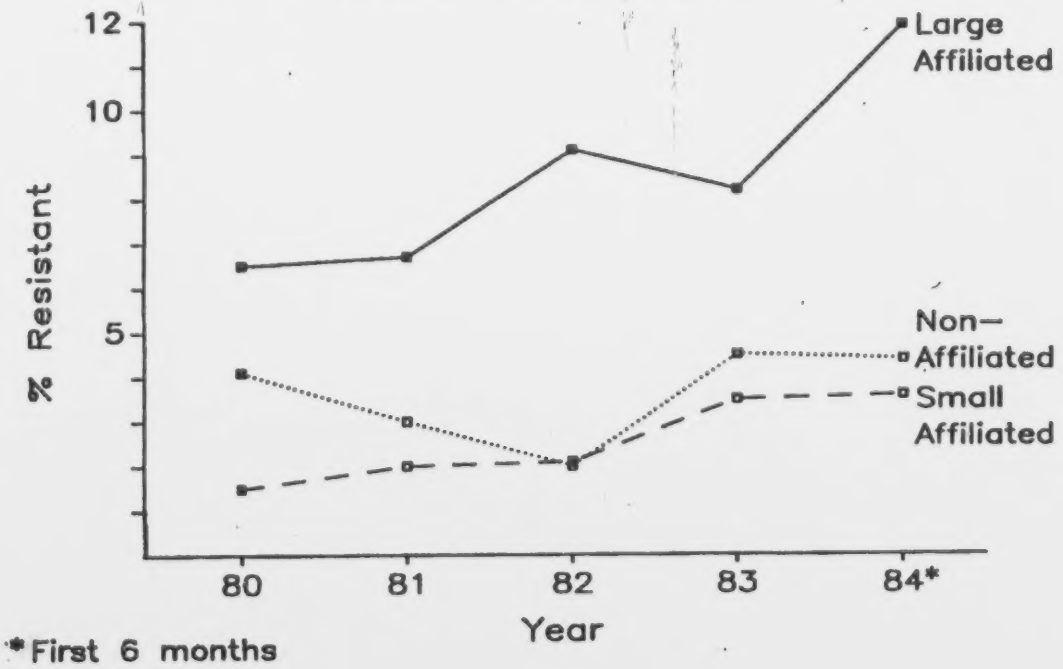
Mr. Chairman, this concludes my formal testimony. I would be happy to answer any questions you or other members of the Subcommittee may have.

Figure 1
Percentage of Nosocomial S. aureus
Isolates Resistant to Methicillin,
by Year, NNIS, 1980–1984



*First 6 months

Figure 2
Percentage of Nosocomial S. aureus
Isolates Resistant to Methicillin,
by Hospital Category and Year,
NNIS, 1980–1984



*First 6 months

Mr. GORE. The final witness on this panel is Dr. Michael Parry, director for infectious diseases and microbiology at Stamford Hospital. And we want to welcome you here, and please proceed, Dr. Parry.

[The biographical sketch of Dr. Parry follows:]

CURRICULUM VITAE

PARRY, Michael Frank, M.D., F.A.C.P.

Birthdate: March 16, 1945
Birthplace: Derby, England

Emigrated to U.S.A. May 27, 1957
Naturalized June 6, 1966

Married - Patsy Jean Callahan, August 24, 1968
Children - Andrea Lynn, born March 28, 1971

Education: Clairemont High School, San Diego, California, 1959-1962
Valedictorian, 1962
Yale University, 1962-1966; English major; B.A. cum laude, 1966
Columbia College of Physicians and Surgeons, 1966-1970; M.D. 1970

Post-graduate Training:

Internship -- Medical, Presbyterian Hospital, N.Y. 1970-1971
First Year Medical Residency -- Presbyterian Hospital, N.Y. 1971-1972
Second Year Medical Residency - University of California Hospitals, San Francisco 1972-1973
Chief Resident in Medicine - Presbyterian Hospital, N.Y. 1973-1974
Fellow in Infectious Disease - Columbia College of Physicians and Surgeons and Presbyterian Hospital, July 1974-June 1976

Hospital Appointments:

Clinical Fellow, Presbyterian Hospital, N.Y., July 1974 -- December 1974
Assistant Attending Physician, Presbyterian Hospital, N.Y. January 1975 - June 1975
Clinical Fellow, Presbyterian Hospital, N.Y., July 1975 -- June 1976
Assistant Attending Physician, Harlem Hospital, N.Y., January 1976 - December 1976
Assistant Attending Physician, Presbyterian Hospital, N.Y., July 1976 -
Associate Attending Physician, St. Joseph Hospital, Stamford, Conn. - July 1976 - July 1981
Director of Infectious Diseases, Stamford Hospital, Stamford, Conn. - July 1976 - 1980
Director of Infectious Diseases and Microbiology, Stamford Hospital, Stamford, Conn. July 1980 -
Attending physician, St. Joseph Hospital Stamford, Conn. November 1981 -

Hospital Committees

Infection Control Committee, Stamford and St. Joseph Hospitals, 1976 --; Chairman, 1977 --
Pharmacy Committee, Stamford and St. Joseph Hospitals, 1976 --
Executive Committee of Medical Department, Stamford Hospital, 1978-1979; 1982-1983
Safety Committee, Stamford Hospital, 1981 --
Institutional Review (Human Investigation) Committee, Stamford Hospital, Chairman, 1981 --
Capital Budget Advisory Committee, Stamford Hospital, 1979 --
Standardization Committee, Stamford Hospital, 1978 --
Laboratory Executive Committee, Stamford Hospital, 1979 --
Advisory Committee of the Medical Staff, Stamford Hospital 1981 --

Academic Appointments:

Visiting Clinical Fellow, Columbia University College of Physicians and Surgeons, July 1970 - June 1976

Assistant Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons, July 1976 - January 1983

Associate Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons January 1983 -

Memberships:

Alpha Omega Alpha, 1970 -
American Medical Association, 1974 -
American College of Physicians, Associate, 1971-1974
American College of Physicians, Member, 1975-1980
American College of Physicians, Fellow 1980 -
American Society for Microbiology, 1975 -
Connecticut State Medical Association, 1976 -
Fairfield County Medical Association, 1976 -
Stamford Medical Society, 1976 -
Fairfield County Medical Association Malpractice Claims Review Panel, 1978-1981
American Society of Hospital Epidemiologists, 1980 -
American Venereal Disease Association, 1981 -
Infectious Disease Society of America, Member, 1979-April 1984
Infectious Disease Society of America, Fellow, May 1984

Board Certification:

National Board of Medical Examiners, 1971
American Board of Internal Medicine, 1974
American Board of Internal Medicine, sub-specialty Infectious Diseases, 1978

Licenses:

New York State, 110495, 1971 -
Connecticut, 18007, June 1976

Honors:

Alpha Omega Alpha, 1970
Teacher of the Year, Stamford Hospital Medical Housestaff Award, 1978
Fellow, American College of Physicians, 1980
Teacher of the Year, Stamford Hospital Medical Housestaff Award, 1982
Fellow, Infectious Disease Society of America, May 1984

Editorial Review:

Annals of Internal Medicine, 1980
Chest, 1980

Editorial Consultant:

Time-Life Library of Health, Coping With The Common Cold, 1981

Dr. PARRY. Thank you, Mr. Chairman.

In addition to my position at Stamford Hospital, I'm associate clinical professor of medicine at Columbia University College of Physicians and Surgeons.

It's a pleasure to be here to discuss antibiotic resistance. The development of new antibiotics has been fostered, obviously, in large part by our awareness of the emergence of resistance in certain bacteria.

The occurrence of resistance is obviously a problem within the past two decades, most notably for staphylococci, as has already been discussed, and also for strains of gonorrhea, Hemophilus and Pneumococcus. Although these resistance patterns have emerged in the community at large, problems within the hospital environment, as mentioned by Dr. Hughes, are clearly a great problem in that environment. Multidrug resistant strains have been recognized there where they're responsible for pneumonia, urinary tract infections, wound infections, and septicemia. In the latter, hospital-acquired context, such drug resistance is frequently due to prolonged hospitalization with invasive procedures, confinement in the intensive care unit, the presence of complicated underlying disease, and our ability to be more aggressive in the treatment of certain other diseases such as cancer with chemotherapy and the consequences related to that chemotherapy. The result of these multidrug resistant infections is increased hospital costs, patient morbidity and, clearly, patient mortality.

The origin of these resistance patterns, both in the community and the hospital, remain somewhat speculative. Clearly, baseline resistance patterns occur in the absence of antibiotic use at all. This has been shown by examining isolates from virgin soil such as the Amazon Basin. Nevertheless, emergence of resistance is clearly related to antibiotic administration both in the community and in the hospital. Obviously a large part of this is unavoidable as a consequence of treatment of any underlying established infection.

The extent to which such antibiotic resistance is real or imagined must be debated. There are clearly trends to resistance among certain species, particularly Staph and gonococci, as mentioned. On the other hand, much of the apparently increased resistance may be generated by isolated hospital-base clusters, case reports, improved technology in being able to uncover these resistant species, and increased awareness of antibiotic resistance by the medical community. This awareness is at least in part supported by developments in the pharmaceutical industry where claims of broader activity are made for newly introduced antibiotics.

Concerted longitudinal studies have been undertaken to show that some of the apparent increased resistance may be due as much to this increased awareness as a real increase in incidence. Exceptions obviously do occur, as in the forementioned penicillin resistance in staphylococci and gonococci, the occurrence of methicillin resistance in nosocomial isolates of staphylococci, and other multiresistant organisms as they appear in the hospital.

It should be mentioned, or perhaps reemphasized, that patterns of resistance vary from one hospital and one locale to another. Antibiotic susceptibility of hospital-acquired bacteria may be significantly less to commonly used antibiotics than to bacterial strains acquired in the community—that is outside the hospital. Similarly, because of differences in patient population and drug use, clusters of resistance among certain strains of bacteria will occur more frequently in a tertiary care center, such as the large hospitals with a medical school affiliation, as mentioned by Dr. Hughes, when compared to the community hospital without that affiliation.

Eighty percent of hospitals in the United States are smaller community hospitals, not the large tertiary care centers. The recommendations for antibiotic use in this environment must be made on data accumulated in this environment and not generalized from results obtained at the tertiary care center.

Two longitudinal studies have recently been undertaken involving over 250 hospitals and 10 million bacteria isolated from patients within the past 10 to 15 years. These were performed under the auspices of Dr. Victor Lorian and the Bronx Lebanon Hospital in New York, and myself at a community hospital in Connecticut.

Dr. Lorian's data were obtained on 10 million bacterial strains isolated from three sources. The first source was Bac-data Medical Information Systems, which is a national bacteriologic monitoring service for hospital laboratories. The hospital laboratories represented by this study are predominantly community hospitals with no medical school affiliation. They vary in size from 150 to 350 beds with a mean of 250 beds. The additional two locales were the Massachusetts General Hospital and the Bronx Lebanon Hospital.

What I would like to show are the figures from these—this article of Dr. Lorian demonstrating the changes in resistance.

Do you want to show these? They are in order.

[Slide shown.]

Dr. PARRY. Obviously, there's a lot of detail on this slide, but all I really want to draw your attention to are the shape of the curves.

In the upper left-hand corner and the upper right-hand corner of this slide are two organisms E. coli and Proteus mirabilis. These are members of the Enterobacteriaceae, essentially bowel flora.

And the curves illustrate essentially a horizontal line for most antibiotics going from 1971 to 1982.

Mr. GORE. What's the line measuring?

Dr. PARRY. The line measures percent susceptibility on the vertical axis and years on the horizontal axis.

Mr. GORE. All right.

Dr. PARRY. With the top being 100 percent and the bottom being zero.

Mr. GORE. So what that illustrates is that there hasn't been a change in susceptibility?

Dr. PARRY. Essentially no change in susceptibility over the 12-year study for those two organisms. With the exception of Proteus mirabilis on the bottom, the susceptibility to nitrofurantoin does appear to have decreased over this time period. Nitrofurantoin is an antibiotic used for the treatment of urinary tract infections.

On the bottom of the page are susceptibilities to Staph aureus on the left and Hemophilus influenza on the right. And again, for the majority of antibiotics shown, the curves are essentially horizontal. The exception for Staph aureus on the left is the decreasing susceptibility to penicillin G, as has already been mentioned, and on the right, Hemophilus. The two antibiotics illustrated are ampicillin on the bottom and chloramphenicol on the top, again illustrating essentially horizontal curves over this time period of study, 1971 to 1982.

[Slide shown.]

Dr. PARRY. The next slide illustrates four organisms again. The upper left is Pseudomonas aeruginosa, which is an environmental, not a bowel organism, responsible for a large number of nosocomial or hospital-acquired infections. And in general, the curves are reasonably horizontal, with the exception of the fact that the susceptibility to gentamicin and aminoglycoside antibiotic has clearly increased. Those are the black squares which is the third line down if one is at the end of the graph. And you can see that that curve does tail down.

The bottom left is Klebsiella pneumonia, another bowel organism like E. coli and Proteus illustrated on the previous slide. And again, the curves are horizontal. The other right is Staph epidermidis, a skin staph species which shows for most antibiotics illustrated in this study, a gradually increasing resistance or decreasing susceptibility over the 12-year study period. Similar changes are found in Streptomyces fecalis on the bottom right, which is a strep species usually found in the bowel.

These two species do show an increased resistance for a variety of antibiotics over the 12-year study period. But these are usually not major pathogens, although they certainly can be in certain settings, particularly in the immunosuppressed patient or patients with prosthetic devices such as hips and other implantable items.

Mr. GORE. In the upper right graph, what is the line going counter to the trend?

Dr. PARRY. The line going counter is tetracycline, which actually has increased in susceptibility over this time.

Mr. GORE. It may be a dumb question, but why would the susceptibility increase?

Dr. PARRY. Obviously, the answer would be speculative. I think tetracyclines perhaps are being used less frequently for the treatment of serious infections, but that's really speculative. It's really unknown. OK.

Separate studies performed by myself at Stamford Hospital, which is a 300-bed community hospital in Connecticut, shows very similar data.

[Slide shown.]

Dr. PARRY. These slides illustrate E. coli and Proteus mirabilis. And the curves are essentially horizontal, looking at gentamicin, cephalothin, ampicillin, and tetracycline. No real change in susceptibility over this study, which goes from 1976 to 1984. The curves for Proteus mirabilis fit right on top of one another, so it looks a little peculiar, but that's just because the curves don't fit within that space. They're all over 95 percent for each drug at each year.

[Slide shown.]

Dr. PARRY. The next organisms here are Pseudomonas and Enterobacter. Pseudomonas, as I mentioned, is a bowel—is an environmental organism responsible for nosocomial infections. The curves are generally horizontal, although gentamicin resistance has increased from about—susceptibility has decreased from 98 percent to 88 percent over this 9-year study. Carbenicillin susceptibility has remained exactly the same, at 90 percent in 1976, and 90 percent in 1984.

Enterobacter is a bowel organism like Klebsiella and E. coli, indicating no increased resistance over this time period.

[Slide shown.]

Dr. PARRY. The next slide shows the susceptibility of Staph, both Staph aureus and Staph epidermidis. Staph aureus susceptibility remains the same over this time period to oxacillin, erythromycin, tetracycline, and penicillin. Staph epidermidis shows some decrease in susceptibility, particularly to erythromycin, although the other drugs, oxacillin, tetracycline, and penicillin, remain about the same.

I think we'll leave out the last slide.

What this data shows is that, with the exception perhaps of certain streptococcal species and Staph, most bacterial species looked at in Dr. Lorian's data, which includes over 250 hospitals nationwide and 10 million bacterial strains, and my own studies at a community hospital of 10,000 isolates over 9 years, shows little change in susceptibility over the last decade.

Although clearly local hospital-based clusters of resistance have arisen in the last decade and may have serious consequences for the hospitalized, seriously ill patient, susceptibility on a more global scale remains virtually unchanged in the last decade.

Thank you very much.

[The prepared statement of Dr. Parry follows:]

Antibiotic Resistance

Michael F. Parry, M.D.

Interest in infectious diseases and the development of new antimicrobial agents has been spurred by the annually increasing incidence of serious, particularly hospital acquired, infectious diseases, and the emergence of multiple drug resistance in certain bacteria. The occurrence of resistance appears to have become a particular problem in the past two decades, most notably for staphylococcal species, and more recently for strains of gonorrhea, Hemophilus, pneumococcus, and even tuberculosis. Although these resistance patterns have emerged in the community, problems within the hospital environment have been even greater. Multi-drug resistant strains have been recognized as a common problem in many institutions where they are responsible for pneumonia, urinary tract infections, wound infections, and septicemia. In the latter, hospital-acquired context, such drug resistance is frequently associated with prolonged hospitalization, increased hospital costs, mobidity and mortality.

The origin of such resistance patterns, both in the community and in the hospital, remain somewhat speculative. Nevertheless, such emergence of resistance is clearly re-

lated to antibiotic administration, particularly in the treatment of human infectious diseases. Although the use of antibiotics in animal feeds is clearly widespread and long-standing, only isolated instances of resistance can be clearly attributable to this use, such as the recently described outbreak of salmonellosis in Minnesota (New England Journal of Medicine, Volume 311:617, 1984). Use of antibiotics in animal feeds and human medicine has paralleled one another, and except in cases of infection due to animal borne bacteria (eg. Salmonella), it is impossible to separate the relative contributions of antibiotics used in these two separate areas. I believe that the majority of resistance problems that we face currently in human medicine are more likely related to the use of antibiotics in humans than in animals.

The largest impetus to the development of new antimicrobial agents in recent years has been the development of multi-drug resistance in hospital isolates. One of the great concerns is aminoglycoside antibiotic resistance which appears clearly unassociated with the administration of unrelated antibiotics to animal feeds. In numerous reports, localized outbreaks of multi-drug resistant infection occur within hospitals directly related to the exposure of patients to the types of antibiotics used within that hospital. In the community, the administration of large amounts of penicillins may well be responsible for the emergence of resistance in staphylococcal species, and

Hemophilus. The development of penicillin-resistant gonorrhea was a phenomenon seen in southeast Asia, subsequently imported to the United States. This resistance is less likely attributable to any other cause than the promiscuous use of penicillin within the high risk populations of southeast Asia.

The extent to which such antibiotic resistance is real or imagined must be debated. There are clearly trends to resistance among certain bacterial species, particularly those mentioned above. On the other hand, much of the apparently increased resistance may be generated by isolated clusters, case reports, and increased awareness of antibiotic resistance by the medical community. This is at least in part fostered by developments in the pharmaceutical industry where advantageous claims must be made for newly introduced agents. Concerted, longitudinal studies have been undertaken to show that the apparent increased antibiotic resistance may be due as much to increased awareness as to a real increased incidence of resistance. Exceptions, however, obviously occur such as the aforementioned penicillin resistance in staphylococci and gonococci.

Two longitudinal studies have been recently undertaken involving over 250 hospitals and 5 million bacteria isolated over the past 15 years. These were performed under the auspices of Dr. Victor Lorian (Atkinson & Lorian, J. Clin. Microbiology 20:791-796, 1984) at the Bronx Lebanon Hospital and myself at a community hospital in Connecticut. Commonly isolated strains of enteric (bowel) flora, staphylococci, Hemoph-

ilus, and Pseudomonas, showed virtually the same susceptibilities to a variety of antibiotics during the study period. Certain streptococcal species and Staphylococcus epidermidis showed an increase in resistance to some antibiotics. These latter increases in resistance were mostly to the penicillin group of agents and to erythromycin and clindamycin. The latter compounds are rarely used as animal feed additives but frequently used in the treatment of human infections, particularly in the treatment and prophylaxis of infections associated with the intestinal and respiratory tracts. Resistance of these microorganisms to erythromycin and clindamycin coincides with the introduction of the use of these agents and their impact on bowel and skin flora.

Particularly noteworthy was the relatively constant degree of susceptibility amongst the studied microorganisms to aminoglycoside antibiotics, ampicillin, and cephalosporins over this 15 year period. The emergence of penicillin resistance in Staphylococcus aureus was a phenomeonon that seemed to occur between 10 and 20 years ago, and has remained stable in the last 10 years. These findings were similar for large referral institutions as well as smaller community hospitals.

Separate studies at Stamford Hospital, a 300-bed community hosptial in Connecticut show very similar data. This is particularly true with regards to ampicillin and the aminoglycoside resistant isolates. The aforementioned in-

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creased resistance in staphylococcal species to erythromycin and clindamycin was again confirmed at the community hospital. Some differences were noted between the community and the tertiary care center in that certain unusual hospital-acquired isolates seem more likely to be resistant at the tertiary care than the community hospital. Such isolates include Serratia, certain Proteus species, and Pseudomonas, all bacteria associated with hospital-acquired infections, intensive care units, invasive devices, and complicated patients treated previously with a variety of antimicrobial agents.

These studies seem to confirm that with the exception of certain streptococcal species and perhaps Staphylococcus epidermidis, which in most cases remains a colonizing and not infecting organism, most bacterial species show little change in antimicrobial agent susceptibility over the last 12 to 15 years. Although local outbreaks of bacterial resistance do arise and may have serious consequences in the hospitalized patient, bacterial susceptibility on a national scale remains virtually unchanged in the last decade. The persistent use of antibiotics in animal feeds and the introduction of new antimicrobial agents for human medicine does not appear to have influenced antibiotic susceptibility significantly. Localized clusters, particularly in tertiary care centers will be problematic and require antibiotic restrictions and enforcement of proper prescribing habits to limit these occurrences.

Mr. GORE. Dr. Levy, what is your reaction to Dr. Parry's last set of statements?

Dr. LEVY. Well, I think that Dr. Parry mentioned that you really can't look at resistance overall in terms of what's happening in an individual hospital and where you are treating an individual patient. There are local variations. And when you start to look at what really was about 5 million strains that were looked at, that you sort of plateau out or even out the hills and the valleys. And I think that what is important is what's going on in the individual hospital, and I think we heard from Dr. Hughes, and those of us treating our own patients have seen the problems.

So to try to say there isn't a problem or it may not be increasing overall if you look at all strains from these particular hospitals—I see it as somewhat of a surprise that in community hospitals we were not aware that this kind of resistance was already there. And if it's the same as was occurring in Massachusetts General Hospital, the tertiary care hospital, then I think that what we've not been aware of and are made aware of now is that there is quite a bit of resistance in these hospitals, and that explains the concern among the practicing physicians to find an antibiotic to treat his particular patient.

Mr. GORE. So—so your response to Dr. Parry's testimony essentially would be that the—that his methodology obscures significant increases in resistance in specific hospital environments——

Dr. LEVY. That is correct.

Mr. GORE [continuing]. By lumping together too much data?

Dr. LEVY. You take two hospitals, one with and without a resistance, you're going to get a 50 percent already.

I also think it's important to note—and it—it has been interesting to me—that the curves, on the ordinate you're seeing susceptibility indicating that, if you see a drop from 90 to 80 percent susceptibility, it looks kind of squished up there. But actually if you're seeing a rise in 10 percent of resistance and you're treating a particular patient, you're going to begin to get concerned about whether to start with this particular drug or not. And I think that whenever there's a significant amount of resistance in your particular area, then you begin to have to look for the drug that's going to do better than 95 percent, and you're also going to want to have to do susceptibility testing and all of that.

So I think the—the numbers, once you get—to my mind, once you get above 10 percent resistance, means a change in therapy or certainly a great bit of concern. Some people might even take the 5-percent mark.

Mr. VOLKMER. Mr. Chairman? Mr. Chairman?

Mr. GORE. Yes.

Mr. VOLKMER. May I interject?

Mr. GORE. Sure.

Mr. VOLKMER. Will you yield for a minute?

Are you—are you telling me, Dr. Levy, that if we have even a 5-percent resistance factor, that that's too much?

Dr. LEVY. I'm not—yes. I would say that if you have a 5-percent resistance factor and you're treating a particular patient, then you're now concerned about resistance and you will ask for what

the susceptibility is and not just be able to treat with a first-line drug with—and certainly no less than 95 percent of surety.

Mr. VOLKMER. Well, will we ever get the point with a society—where we've been and what was used, when are we going to ever, even if we go to restricting the use of penicillin and tetracyclines and all the other drugs—and they're only serious things—are you telling me that if we do that, we will get 100 percent and 99 percent of susceptibility?

Dr. LEVY. This is, of course, a question we'd all like to have an answer for. I think that from studies we've done in isolated environments, it takes a while for susceptibility patterns to come back. And that indicates to us that the rise in resistance, the antibiotic is a great—greater selective force for bringing these bacteria in large numbers in the environment killing off all the others. But the return back again requires competition with susceptible strains that now can get back into that environment.

I think that we can see reduction definitely. But to get back to 98 percent, we may not, or else it would take quite a bit of time, as long as we're still able to use the drug. But I am concerned, as are others, that as new drugs get introduced, that we will quick—quickly surpass the 90-percent susceptibility.

Mr. VOLKMER. Dr. Parry, did you have something you wanted to say?

Dr. PARRY. Yeah; I—I would like to second what Dr. Levy said. There are some flaws, obviously, in looking at the data the way I—I presented it. I presented it that way because that's the way it's usually presented and that's the way Dr. Lorian's data was published. But——

Mr. GORE. Can you use the mike.

Dr. PARRY. Yes.

Mr. GORE. Yeah.

Dr. PARRY. If you decrease susceptibility from 99 to 96 percent in a particular organism, that doesn't look like much. But if you turn it around and say that's resistance from 1 percent going up to 4 percent, that's a fourfold increase in resistance, which may be significant depending upon the type of organism, the sort of infection you're dealing with in a given patient.

So I'm not presenting this data to say that there is no problem. I'm presenting it to say that, in general, the trend has not been inexorably downhill.

Mr. VOLKMER. In other words, we—what—if the chairman would yield further—what we're basically saying is that we may have gone from—20 years ago or 40 years ago when we started using penicillin, we may have gone from 100 percent down to in some instances 95, some to 90, some to 88; is that correct?

Dr. PARRY. Yeah; that's the trend——

Mr. VOLKMER. I mean if we assume that when we first started using penicillin that there was no resistance to it, if we assume that.

Dr. PARRY. Right.

Mr. VOLKMER. I'm not—I don't know if I'm ready to assume that, though. But assuming that, are we—what you're saying, Dr. Parry, is that we haven't gone real far yet. The question is—and we haven't really in the last 9 years——

Dr. PARRY. Nine, ten years.

Mr. VOLKMER [continuing]. Dropped any further. And there's probably been a heavier use of these drugs in that time period and—and different new drugs.

Dr. PARRY. I think, as a generalization and a sort of conceptual statement, I think that's true. Obviously——

Mr. VOLKMER. We've had more new drugs in that period than we had in the previous period.

Dr. PARRY. That's certainly true.

Mr. GORE. Well, it—it depends on when you start measuring from, because I notice from your viewgraphs that Staphylococcus aureus has about a 10-percent resistance to penicillin. Susceptibility——

Dr. PARRY. No; 10 percent susceptibility.

Mr. GORE. Susceptibility of 10 percent and a 90-percent resistance to penicillin——

Dr. PARRY. That's true.

Mr. GORE [continuing]. At this point.

Dr. PARRY. That's why I said the concept is true, the numbers will differ depending on the organism.

Mr. GORE. Well, is it fair to assume that if you went back 30 years Staphylococcus aureus had a——

Dr. PARRY. A much higher susceptibility.

Mr. GORE [continuing]. A much higher resistance—I mean a much higher susceptibility to penicillin?

Dr. PARRY. Absolutely.

Mr. GORE. A hundred percent did it start off at?

Dr. PARRY. Not 100 percent; it started out over 50 percent.

Mr. GORE. Yeah; so now it's down in—in just a couple of generations, it's down to—to 10 or 15 percent.

Dr. PARRY. That's right, if you go back far enough. Looking at the last 10 years it's leveled off, but if we go back 30 years, it's clearly become a problem.

Mr. GORE. And in your same—and you have Staphylococcus epidermidis where all four of the antibiotics that you measure are below 80 percent now, and penicillin is—is below 40 percent susceptibility.

Dr. PARRY. That's correct.

Mr. GORE. Penicillin has been the most widely used antibiotic over the longest period of time, and these numbers ought to be cause for real alarm, shouldn't they? Shouldn't they be?

Dr. PARRY. Well, yeah, I agree to some extent that's true.

Mr. GORE. To some extent? What—how—tell me—tell me—tell me—tell me why they shouldn't be cause for alarm? What would—what would—what would mitigate the—the concern there?

Dr. PARRY. Well, I think that the understanding of penicillin resistance allows the development of a drug which would be useful in the context of penicillin resistance, such as oxacillin, for example.

Mr. GORE. Yeah.

Dr. PARRY. So——

Mr. GORE. Is that o-x-a?

Dr. PARRY. That's o-x-a.

Mr. GORE. That's down below 80 percent now for this——

Dr. PARRY. That's true for Staph epidermidis, which is usually a colonizing organism.

Mr. GORE. Yeah.

Dr. PARRY. I think it—it emphasizes the fact, obviously, that resistance does occur and is a problem. It goes hand in hand with, I think, antibiotic development so that we develop antibiotics which will be effective against these—these isolates.

In my 9 years at Stamford Hospital, there has always been a drug which is effective against an isolated organism. I haven't lost patients because of ineffective drugs. I might prefer to use a better drug or a less toxic drug, but despite the evolvement of resistance over this time period, there have been alternate drugs to use.

Mr. GORE. But—but it's also—I mean it's also a cost issue——

Dr. PARRY. Sure.

Mr. GORE [continuing]. And it's also a question of what makes the most sense to—to continue our—our hope that this magnificent pharmaceutical industry we have can continue to come up with ever more potent miracle drugs or to take sensible measures to conserve the—the susceptibility of the disease organisms to—to the arsenal of antibiotics that we now have. Isn't that the more sensible course of action that we ought to be pursuing, even as we encourage these companies to develop more potent antibiotics?

Dr. PARRY. Sure. I guess it's just a question of—of—of where you say is it concern or is it great concern. It's obviously concern because there is resistance.

Mr. GORE. Well, but your—but your testimony and—and the study that—that has been done by Barbara Atkinson and Victor Lorian, which has been cited by every representative from—from the industries that are affected by this—the study and your testimony both are—are heard by people as a statement that we don't really have to worry about this because the susceptibility of—of bacteria to antibiotics is not increasing very much. I mean, that's—when I—when I listen to your statement, it's—it's—it's balanced, carefully stated and all the rest. But the thrust of it is, don't worry very much about this because the resistance is not increasing very rapidly. I mean, is that—is that an unfair interpretation of what you're saying?

Dr. PARRY. No; it's not totally unfair. I think the data, as presented, show that there is a general plateau of susceptibility and resistance to most antibiotics in these particular bacteria.

Mr. GORE. But the medical consequences—I mean, if you put it in the medical context, even small decreases in susceptibility force physicians to abandon one antibiotic—maybe abandon is too strong a word—but to stop using one antibiotic for their patients and go instead to a more potent one.

Is—I mean, look at—let's look at gentamicin as an example. You have a—one of your charts on Pseudomonas, for example, shows a—wait 1 minute. Let me see. Which one is that that I was looking at. One of the—one of the charts shows a fairly small decrease in the susceptibility to gentamicin. Yeah, Pseudomonas. And all of a sudden, even though that decrease is kind of small, it can't be used anymore. The doctor just will not trust it to—to—to be used in his patients, so—so—so they—it has to go to something else. Isn't that the—isn't that the practical consequence of it?

Dr. PARRY. Yes; as I said, going from 99 percent to 96 percent—
Mr. GORE. Yeah.
Dr. PARRY [continuing]. Is a fourfold increase in resistance.
Mr. GORE. Yes.
Dr. PARRY. That is significant.
Mr. GORE. Yeah.
Dr. PARRY. Whether that's significant enough to abandon the drug is another question. Our hospital, for example, accepts 90 percent to 95 percent susceptibility as being adequate coverage in most situations. Now the clinical illness will dictate how much leeway you have. If you're treating a urinary tract infection that's causing just bladder problems without bloodstream infection, I would be willing to accept a 20 percent error rather than go to a more costly or more toxic drug.
Mr. GORE. Well, what I'm saying—I don't think anybody's suggesting that we just abandon the antibiotics. What's being suggested is that we take a number of steps to conserve the susceptibility of bacteria to the whole—the whole arsenal that—that we have. And I—I guess I'm just a little concerned that—that—that these things—that—that—these graphs and charts and other evidence be presented in a careful way so as not to minimize the—the practical consequences of eroding the susceptibility of bacteria to antibiotics. As a practical matter, the erosion which has already occurred appears to be quite—quite significant. Would you agree with that statement?
Dr. PARRY. Yes; I wouldn't disagree with that at all.
Mr. GORE. Yeah.
Dr. PARRY. As I said, the flaws in the study are its limited time period, which is 10 years or 15 years at most, which misses most of the increasing resistance of Staph to penicillin; the 90 percent presenting concept instead of presenting from zero to 10 percent resistance which, obviously, is a much more graphic way and certainly illustrates the importance of resistance emerging, particularly in the hospital environment. I think both of those two things limit the data that I present, as I said.
Mr. GORE. If we cut back on misuse of a particular antibiotic, one would expect that antibiotic to become more effective over time; is that correct?
Dr. PARRY. One would expect that.
Mr. GORE. So even if there's a flat curve now, that's—that's not the entire issue, because conserving the susceptibility in cutting back on misuse and overuse can have the effect of—of increasing the susceptibility of bacteria to—to antibiotics.
Dr. PARRY. That's a theory that—I mean, it sounds good, and I would expect that, but——
Mr. GORE. Well, if it's not—I mean, I, you know——
Dr. PARRY. Well, we don't really know. That's the problem.
Mr. GORE. OK. Fair enough.
Dr. PARRY. I mean——
Mr. GORE. Fair enough.
Dr. PARRY [continuing]. I think we know in some settings, but—and we would anticipate it, but we don't really know for a fact.
Mr. GORE. Dr. Levy?

Dr. LEVY. Well, I think there have been studies in hospital settings. And in a nursery in which kanamycin resistance was a problem, they switched to gentamicin and kanamycin resistance was no longer a problem.

There is a study out of England where carbenicillin resistance was a problem in Pseudomonas infections in a burn unit, and they did the courageous thing of stopping all antibiotic use there and the organism went down.

So I think that in isolated settings, the removal of the selective pressure will cause that organism to go down. Now if that is not the selective pressure, you see, you're making no charge. If it is the selective pressure, it makes sense, because you remove it, and then the normal compet—competition between the organism and that environment will then settle out and, from what we understand, susceptible strains not carrying a little bit of extra material will come back.

But if there's some other factor such as poor sanitation, poor public health, whatever it is, then just removing the antibiotic once you have the strain there——

Mr. GORE. Yeah.

Dr. LEVY [continuing]. May do nothing.

Mr. GORE. So even though resistance may—may dissipate or may erode fairly—at—at—at a more rapid rate, the return of susceptibility when you remove the evolutionary pressure to—for resistance genes is going to come—it's going to come back at a slower pace typically. Is that——

Dr. LEVY. That is correct.

Mr. GORE. Anybody disagree with that?

You would not—you would not expect the resistance gene to be selected out in the absence of the antibiotic pressure. In fact, it would confer a disadvantage on the—on the bacteria—theoretically it would.

Dr. LEVY. I—I wish we knew more about that. I think what we do know is that if you use the antibiotic in that setting, there's no question the resistant organisms are going to survive and they're going to multiply.

But now you have selected out this one bacterium or group that are now living there. Now remove the antibiotic. Theoretically that one little gene should make no difference. But what you don't know is, if you've taken this organism which just happened to have the gene, let's say, for gentamicin resistance, but it's carried on a big plasmid that might have other genes on it——

Mr. GORE. Yeah.

Dr. LEVY [continuing]. That say hey, I like this environment.

Mr. GORE. Yeah.

Dr. LEVY. I'm going to stay here. And I won't lose that gentamicin resistance marker for a while because it's not being selected against, so to speak. And so that's where the problem arises. It's once you select the organism, you select everything it has with it.

And that's why when we use one antibiotic, we inadvertently select an organism that carries along with it resistance to other antibiotics. They're not even in that environment, but they're carried on the same plasmid along with many other genes which—well, what many of us are trying to find out is what are they

doing? They're obviously carried by the bacteria because it helped them to survive in that environment, if it's in the drain pipe or in the gut of somebody or on tables. And these are what I call the survival traits which are important for the survival of the bacteria, and the resistance, at the moment of antibiotic use, is one of those survival traits.

Mr. GORE. All right. Very good.

Mr. Volkmer.

Mr. VOLKMER. Yes; I would like to ask questions in regard to—Dr. Parry, on your charts here, the E. coli—if I was a medical physician and had this information, I wouldn't use probably anything but the top figure here, which is the gentamicin for treating that, would I?

Dr. PARRY. Well, it depends what you're treating. If it's an E. coli and it's a bladder infection——

Mr. VOLKMER. Right.

Dr. PARRY [continuing]. You wouldn't want to use gentamicin in an outpatient because you have to give it by injection and it's got a lot of side effects.

Mr. VOLKMER. All right.

Dr. PARRY. So you take the 10 percent or 15 percent resistance and use ampicillin, which is inexpensive and has no side effects unless you're allergic to it—or minimal side effects.

Mr. VOLKMER. Can somebody there explain to me why in these we show no decline for some of them, and some of them we do? I mean, I can go through about every one of these charts and find something on each one of these micro-organisms in the—except, I guess, on the Staph epidermidis. There is a decline about in all except the—which one was that, the tetra—the tetracycline.

Dr. PARRY. I—I'd defer, I guess, to Dr. Levy in terms of the molecular reasons for that, except that we do note that increased resistance to some drugs and not to others.

Dr. LEVY. Mr. Volkmer, I think part of the reason is that what you're seeing on the graph is resistance to a single drug in an organism, but you don't know what else the organism has. Perhaps that same bacterium has resistance to ampicillin, gentamicin, and tetracycline. Now you stop the use of tetracycline, but the organism is still there because it's responding to the use of ampicillin or gentamicin.

What's not presented in these graphs is the increase—and Dr. Parry mentioned that—of multiple resistance. It's not just the single drug in the bacterium, but it's carrying other resistances. So you might stop one of the three that it's resistant to, but the other two will maintain that organism, and all you're asking is that it should lose that other resistance.

Now I don't know what the reason is for the drop in some and the plateau in the others, but there are lots that we know about how these genes exchange and what's on them to be able to say well, that's one possibility. And the possibility is also that the mechanism, for instance, of tetracycline resistance is putting a protein in the membrane. And in most of these bacteria, it is so toxic at times, unless it's required, that the cell doesn't produce that protein unless it sees tetracycline. So it's very likely that that gene is

not doing much good to the bacterium until it needs it. So that might be lost a little more quickly.

These are the kinds of questions, those that you're raising, that I think are important to our understanding of how we're going to reverse the situation. I think we know a lot about what can happen, but we don't know exactly whether that's what's going on in that particular bacterium or not.

Mr. VOLKMER. Well, certain bacteria have certain resistance to certain medications rather than others; is that—is that——

Dr. LEVY. That is correct.

Mr. VOLKMER [continuing]. Correct? And that's been time eternal.

Dr. LEVY. But we have seen probably in the first 5, 6 years of use of these drugs the rapid emergence of resistance, and then maybe there's a little plateauing in an area that, once you use the drug, it'll go up again, then it comes back down again.

What we don't see is that every time you stop the drug and you go back to another lower level due to the competition between susceptible and resistant strains, you don't know where that level is. And then you get into that environment again and add the antibiotic back again, it jumps up again, and you're constantly asking that bacterium to be ready for the onslaught of that drug.

I don't think that it's—anyway, I think that in these cases where your levels slowly move up so that, even randomly looking at the organism anytime, with or without antibiotics, you'll see it at a certain level. If you give it antibiotic, it should be in the high levels because nothing's going to survive that drug.

Mr. VOLKMER. Dr. Hughes, in the studies of the hospitals and the problems there, do we ever see any change over a period of years in the infectious rate, et cetera, in those hospitals?

Dr. HUGHES. You mean in the overall nosocomial infection rate?

Mr. VOLKMER. Yes.

Dr. HUGHES. Yeah, that's——

Mr. VOLKMER. I mean in this—in an individual hospital, does it go up and down or just stay steady or——

Dr. HUGHES. It varies from hospital to hospital. Some—some data from another study that I've—that I've not alluded to here at all today suggests that, overall, in the absence of any efforts in a hospital directed at controlling hospital infections, you can expect something on the order of about a 15-percent annual increase in the infection rate.

Of course, there are—there are not many, if any, hospitals in the country that don't have an infection control program. So that's—that's not happening today in 1984. But in the absence of infection control efforts, you can expect to see increases in nosocomial infection rates, as well as presumably increases in frequency of—of resistance in some of these nosocomial pathogens.

Mr. VOLKMER. But, my question again—I'll go back to it. Does—is it a—if you do have controls and you do maintain it, do you see—see a decline in those hospitals, or do we still see—every once in a while see an increase?

Dr. HUGHES. OK. What the national surveillance data that I have talked about show is that the overall nosocomial infection rate for the past 8 to 10 years has been fairly constant. During that

period of time, there have been more intensive efforts made at controlling the spread of nosocomial infections on the one hand. On the other hand, as you are well aware, the sophistication of medical technology has increased during that time. So I feel that those two trends are, to some extent, balancing each other.

Mr. VOLKMER. OK. Dr. Parry and maybe—because both you and Dr. Levy have alluded to questions that we are addressing also and addressed yesterday in use of antibiotics in animals and animal feeds, et cetera, like that. And many of these medications we've had here are not used in animal feeds, are they not?

Dr. PARRY. Yeah, they are. I'm not exactly——

Mr. VOLKMER. Some of them are and some of them are not.

Dr. PARRY [continuing]. Sure. I think mostly the penicillins and tetracyclines, yeah.

Mr. VOLKMER. I mean other than those—I mean——

Dr. PARRY. Aminoglycosides are not, as far as I know, used in any animal feeds.

Mr. VOLKMER. Yet, we do see resistance factors there also?

Dr. PARRY. Certainly.

Mr. VOLKMER. Maybe use some in therapeutic but not in subtherapeutic? Some of them are not used altogether is that correct?

Dr. PARRY. In animal feeds. Are you talking about animal feeds now?

Mr. VOLKMER. Right.

Dr. PARRY. As far as I'm aware, aminoglycosides are not used in animal feeds, but I'm not an expert there. I wouldn't——

Dr. LEVY. Streptomycin is an aminoglycoside, and that is used.

Dr. PARRY. In animal feeds.

Dr. LEVY. That's correct.

Mr. VOLKMER. Well, I don't know—like beef or—we continue—we do see resistance factors in those that are not used also; is that correct?

And, Dr. Levy, do you have any comment you wish to make on the Lorian—Dr. Lorian's report—comment on Dr. Parry's?

Dr. LEVY. I have seen Dr. Lorian's paper, and I have—actually I was responding to that as much as to Dr. Parry, because I think the point that was being made was not the points I got out of the paper. The point that was made was that susceptibility has not changed, therefore, we're doing something right.

And when I looked at the data, first of all, I realized that they were mostly community hospitals with what I saw was a lot of resistance.

Second, as Dr. Parry brought out, my comment was that when you look at resistance that goes from 1, to 4, or 5 percent, that's a problem. It's like if you're in that hospital and you see resistance rising, you're beginning to wonder why. That's an alert. I mean do we think that crime prevention is any better because it stays at 95 percent and then goes down to 90 percent? Are we going to say that that's no—we don't have to worry about it? No; we're going to worry about that extra 5 percent, or even if it's another 0.5 percent. We're not getting any better. So that's the way I regard this report.

In addition to the fact that I think, while it's impressive in its total breadth, it's really looking at everything all over, and I don't

think that really ties into the individual physician or the patient. What good does it do you as the patient who's dying of a resistant infection, or costing lots of money, or having side effects if the study says that there's only 20 percent resistance or 10-percent resistance? You have that organism. And may be in that hospital it's a little higher.

So I think it gives a false impression, and that's what upset me about the conclusions of that study. The data, as such, are of some interest. But, as I said, I interpreted them differently.

Mr. VOLKMER. All right.

My question, Dr. Levy, is should we discontinue the use of penicillin for therapeutic treatment of human beings?

Dr. LEVY. Absolutely not. I'd love to see it come back, to be able to be used more frequently.

Mr. VOLKMER. Well, if you use it more frequently, aren't you going to create further resistance to genes in the microbes, in the bacteria?

Dr. LEVY. I think I probably should have added, prudently or wisely, since I think that in all areas of use, if you look at the studies, there's a tremendous amount of misuse which can even amount to 50 percent. So if we use penicillin when it's appropriate and tetracycline when it's appropriate, and not when it's inappropriate, we will be doing just what you want, and, I think, is making the drug now useful in its appropriate setting, recruiting susceptible bacteria who are not being devastated or the resistant ones coming up in environments where they're being used indiscriminately, and I think we'll have come back to a time where many of these nontoxic, very good, older antibiotics are useful.

I think it also goes for the newer ones. It's fantastic the new drugs that are coming into use. They're treating infections well. They are being used at less time sequences. We're able to use them in certain cases orally rather than being needed for hospitalization. But they run the same risk. The genetic fluidity has been evident to us. And while Dr. Hughes had mentioned that resistance to third-generation cephalosporins is not a problem in a sense that it's causing an overall national problem, at individual hospitals, it can be. So you really want to start to change the feeling, increase the awareness, that these drugs cannot be just tossed out and given, as I said, the mother on the bus, the woman or man who keeps it in their pocket and they get a little cold and can't afford to have an infection, so they take one pill. They're just creating that environment.

Mr. VOLKMER. What—let's see. Put it this way. Staph—let's take the Staph first, the general area of the family of Staph. This goes to Dr. Parry or Dr. Levy. It doesn't make any difference to me.

Those transmittable from human to human, correct?

Dr. LEVY. Yes.

Mr. VOLKMER. And also by—some of them by environment——

Dr. LEVY. Yes.

Mr. VOLKMER [continuing]. In humans? All right.

What about the Strep, the same way?

Dr. LEVY. That is correct.

Mr. VOLKMER. How many of those are transmittable by animals to human, Staph or Strep?

Dr. LEVY. I can't give you an answer on that.

Dr. PARRY. Both.

They're not really environmental. I mean, they would be human or animal——

Mr. VOLKMER. Yeah, but you——

Dr. PARRY [continuing]. To human.

Mr. VOLKMER. Can you not shed it and have as an environment, in other words——

Dr. LEVY. The Strep—the Strept——

Mr. VOLKMER [continuing]. Like the hospital or something like that?

Dr. LEVY. You can pick them up from the environment. You can deposit them in the environment—by both animals and man. The question in interpreting, is where is it happenings the most—when we've looked at these studies, the Staph to Staph spread has been mostly localized in hospitals where these infections have occurred. In theory, sure you can pick them up. And in certain studies, looking at the enterococcus, for instance, in farms, they've shown that you can pick it up from the animals, mostly the gut bacterium, because they've looked at it. But in theory, there should be nothing different about them in terms of whether they can or cannot. Some are better adapted to animals than man, but the same kinds can exist in man, and animals, and in the environment. They have to persist somewhere, and they are not always persisting in the animal or man.

Mr. VOLKMER. Now, Dr. Hughes, in your—in your studies, an example not in the general overall hospital, but, say, in a single hospital which you studied, are there ever antibiotic resistance patterns seen? I'm sure the answer to that is——

Dr. HUGHES. Sure. I mean every——

Mr. VOLKMER [continuing]. Yes.

Dr. HUGHES [continuing]. Hospital——

Mr. VOLKMER. Right.

Dr. HUGHES [continuing]. Every hospital has some sort——

Mr. VOLKMER. As an individual hospital, right.

Dr. HUGHES [continuing]. Problem with antibiotic resistance in some strains of bacteria.

Mr. VOLKMER. Now do they change?

Dr. HUGHES. In some hospitals, they certainly do.

I should point out that when I was talking about the group of large medical-school-affiliated hospitals on the one hand versus other hospitals, that's not to say that all large medical-school-affiliated hospitals have the same sort of problems or that the incidence of problems in those hospitals is changing at the same frequency in all hospitals. There's variation from hospital to hospital, certainly.

Mr. VOLKMER. And have—have we found, Dr. Levy, that at certain times in our history of use of antibiotics, that that antibiotic on a given—I don't know what to say—microbe or bacteria, it may be more susceptible or less susceptible, and then change around and come back the other way?

Dr. LEVY. No question.

Mr. VOLKMER. What can you attribute that to? I'm just, you know——

Dr. LEVY. I—I——

Mr. VOLKMER. You can spec——

Dr. LEVY. Bacteria, before antibiotic——

Mr. VOLKMER [continuing]. Speculate if you want to.

Dr. LEVY. Before antibiotics began to be used by man—and remember, we're only talking about four decades. I think this is what's impressed us from the genetic standpoint, is the tremendous variation, and we've learned an awful lot about genetics from this phenomenon. It's a tremendous clinical—I think, clinical problem, but it's also surprised us.

The writings, for instance, of Fleming during the forties saying we've got to be careful about resistance to penicillin because they'd already picked it up. It was about 14 percent 3 years after it was introduced in the hospitals, but in the community, it was working great when it was available.

But I think the point is bacteria had these little circular molecules or plasmids for other purposes. And if you go back before antibiotics were used, you'll find they're still there. We went into the jungles of Kenya and looked at primates, baboons, and we found bacteria and they all had their plasmids, no resistance. And if you look at these plasmids, as Dr. Naomi Datta did in England, they're the same kinds as we're finding now, only now they have these extra pieces of DNA, may represent only 1 percent of the plasmid total material, and they are resistant. So what we're saying is they're being added on.

But those plasmids are there so these bacteria can live in your gut, do something with the materials, kick it out, keep it in, survive in water when they're deposited there, or survive on sludge. And the fact that they have the extra resistance gene is like they're picking up a metal resistance, for instance, because they're deposited where there are heavy metals. I mean, there is this—the genes are out there. You put a selection, you'll get the 1 of 100 million, 1 billion. That organism now comes back and takes over. But it's now a new major component of the environment which now has its normal plasmid, it's added on that resistance to the metal, it may add on a resistance to an antibiotic.

But the major genes there are probably the other genes on that plasmid. And if we knew more about them—some we know cause adherence, some are grabbing on to iron and other genes. If we know more about them, we perhaps can understand better how we could eliminate the plasmid in a general population. But I think that's going to be very difficult, mainly because even these resistance genes, they don't have to last on a plasmid, they can jump onto the chromosome. And if you're going to get rid of the chromosome, you might as well just use the drug that's going to kill the bacterium. That's what you're doing.

Mr. VOLKMER. Last question, and maybe give me a little more speculation, and that is will or will not bacteria—or maybe I should say "could" instead of "would"—develop resistance genes to certain drugs in a span of man—as man continues to develop, because that's what basically we're doing—even without the application and use of that drug?

Dr. LEVY. Unless that particular resistance offers them the ability to survive in that environment, we're just really going back to Darwin's theory of survival of the fittest. No; it might be there. We

have demonstrated that within the chromosome of E. coli, a normal inhabitant of the gut, there are genes for resistance to many antibiotics that are not expressed until we adapt the strain to those drugs. They're there for some other purpose.

Now why are they still being held onto in the chromosome of that bacterium? We don't think it's because they had been seeing these drugs before. They're doing something else. As I said, tetracycline resistance is caused by the pumping out of the drug. Well, it may've been there for pumping out something that looks like tetracycline that's seen in the environment.

My answer is that the genes are there. They may not be in large numbers. They may be even hidden. They need one little mutation and then they're expressed. We have seen this in certain chromosomal genes that are now being induced to resistance to the newer penicillins that are not broken down by the enzymes, and these genes are hidden in the chromosome. They're being amplified. They weren't being seen before.

So I think what—if I can interpret your question, it falls into what I see as that we can't assume the bacterium is going to just sit back and let us hit it with an antibiotic for which it's not going to somehow develop a resistance. It's a simple organism, but the——

Mr. VOLKMER. No; I didn't make myself clear, or maybe I should put it this way: Aren't there bacteria that develop over a period of time in different strains of bacteria over different periods of time?

Dr. LEVY. Well, it would be long periods of time, certainly not within our lifetime. And I think that what they do develop are new plasmids which give them those extra genes they didn't have before.

Mr. VOLKMER. And where do those develop?

Dr. LEVY. They come from being picked up from other bacteria. You have bacterium A, B, C carrying their genes on plasmids, and they can be interchanged. So now you create a new bac—the same bacterium. The bacterium is still called whatever its species is——

Mr. VOLKMER. But it has a new property.

Dr. LEVY [continuing]. But now it carries something else.

Mr. VOLKMER. It has a new property.

Dr. LEVY. That is correct. It has a new property. It can now exist in a new environment. It can now resist a drug. It didn't have that before.

Mr. VOLKMER. The question I get back to, did it take an application of an antibiotic in order to create that new one?

Dr. LEVY. I think that it did in the case of certain bacteria that we see now. For instance, Haemophilus which is bearing the gene for resistance to penicillin that was seen in the gut bacteria for so long ago. I don't see that rare event must have occurred because we had so many of these genes in all the organisms otherwise. We looked for it. We looked for it in Neisseria, we didn't see it. And I think that these are the strong selective pressures of antibiotics will allow those rare events to occur. And once they've occurred, you have an organism which is now established in the environment. As I said, it then can be transported, but it has a gene in it now that's going to be allowing it to survive in environments that it had not survived in before, and then it's just going to increase

and multiply, so that it now becomes a problem in different areas of the world and in different States of our country.

Mr. VOLKMER. But only within certain hosts. Not everybody—you know, I don't want to prolong this all day. It's interesting—but not everybody would be a host to develop that same——

Dr. LEVY. That is correct.

Mr. VOLKMER [continuing]. Gene. Right.

Thank you very much, Mr. Chairman.

Mr. GORE. Thank you.

I have just a couple more short questions. First, Dr. Parry, is it fair to say that—and I'll ask Joe Stetler about this in the next panel—but is it fair to say that the more powerful antibiotics that have had to be created because of the—because of the declining resistance are generally associated with more side effects than penicillin, tetracycline and some of the earlier compounds?

Dr. PARRY. Some of them.

Mr. GORE. OK; I'll—I'll—I'll come—I'll get—I'll—I'll—I'll come back to that in the next panel.

Dr. Levy, you used the word transposons. I—just when I thought I understood this——

Dr. LEVY. I'm sorry.

Mr. GORE [continuing]. And was talking in terms of plasmids, you come up with transposons. Now is that something out of D.C. Comics, or is that a real——

Dr. LEVY. Gee, I should read D.C. comics, yes. The——

Mr. GORE. The transposon.

Dr. LEVY. The transposon is a small—it's an even smaller piece of DNA which can jump from a plasmid onto a chromosome. And you—what's unique about it is that it doesn't need a particular bacterial species. Some of the plasmids can only exist in one bacterial species and not another. But many of them get into another species, and then they are lost. But that transposon, especially by a certain frequency, will jump onto the chromosome or onto another plasmid which is already established in that particular host.

So I think that this makes the level of transfer that much more expedient, because you don't need not to just have the plasmid. I think this is where trying to get rid of plasmids is not necessarily going to be the answer, because you can get rid of the plasmid, but if it's jumped onto the chromosome——

Mr. GORE. Yeah.

Dr. LEVY [continuing]. It's not going to work.

Mr. GORE. I see.

Does this—does this, in part, explain how bacteria acquire resistance to several different antibiotics at the same time?

Dr. LEVY. That is correct. These are on individual transposons or together, and they can jump en mass or individually onto a resident plasmid. And you see instances where a single plasmid will initiate with one resistance and then will accumulate others.

Mr. GORE. OK.

Dr. Hughes, should the voluntary CDC surveillance program be made mandatory?

Dr. HUGHES. Oh, no, I don't think so. I think that we're very pleased with the cooperation that we—that we receive from these hospitals.

Mr. GORE. Do you have adequate access to information?

Dr. HUGHES. Oh, yes; and this has been—this system's been in existence for 14 years.

Mr. GORE. Yeah.

Dr. HUGHES. We have other hospitals interested in joining. So I—I don't see any reason at all to make it mandatory.

Mr. GORE. Good.

Now your statement that one-third of the infections that would occur in hospitals could be prevented by well organized programs was a little unclear to me. Does this mean that more of the programs—more such programs are needed, or does it mean that nosocomial infections would be one-third greater without the programs already in use?

Dr. HUGHES. Well, most hospitals—in fact, essentially all hospitals have infection control programs. And so hospitals have all—have already progressed along towards this ultimate one-third potential prevention.

I think we need to—to help hospitals in terms of providing them with additional information to allow them to make their programs more efficient. That's what we're trying to do.

Mr. GORE. A couple of years ago, this subcommittee almost had a set of hearings on nosocomial infections. Are there things that you would recommend that we do as part of a national policy to address this? I mean, clearly the cost implications are enormous.

Dr. HUGHES. Well, the cost implications are—are enormous, certainly. I think that hospitals have acted extremely responsibly in this area. And I think that tremendous progress has been made in the last 15 years in preventing nosocomial infections. I think there's more yet to be done, but I think hospitals are doing a good job.

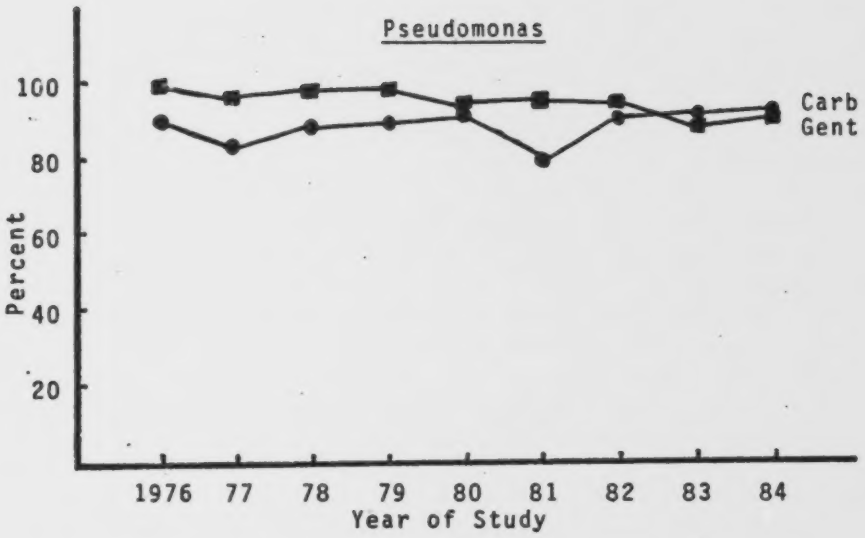
Mr. GORE. Why is the risk higher in large hospitals affiliated with medical schools and lowest in small unaffiliated hospitals?

Dr. HUGHES. OK. I think the—the explanation for the overall higher nosocomial infection rate in the large hospitals—not talking about antibiotic resistance now, just talking about the nosocomial infection rate in general—I think that's higher because that's—it's higher in those hospitals because the average patient's risk of nosocomial infections is much higher in those hospitals. Those—those are the tertiary referral hospitals where the sickest patients go, and they're the hospitals, by and large, that have the burn units, and the trauma units, and the sorts of critical care areas where—where the sick patients are and the ones who are most at risk for developing infection.

Mr. GORE. OK.

Without objection, we're going to make the—the vu-graphs a part of the record at this point.

[The vu-graphs follow:]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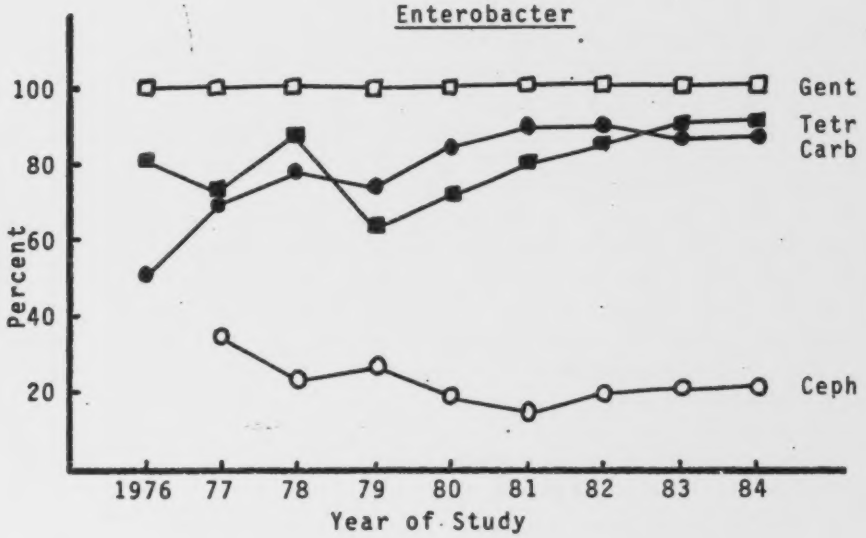
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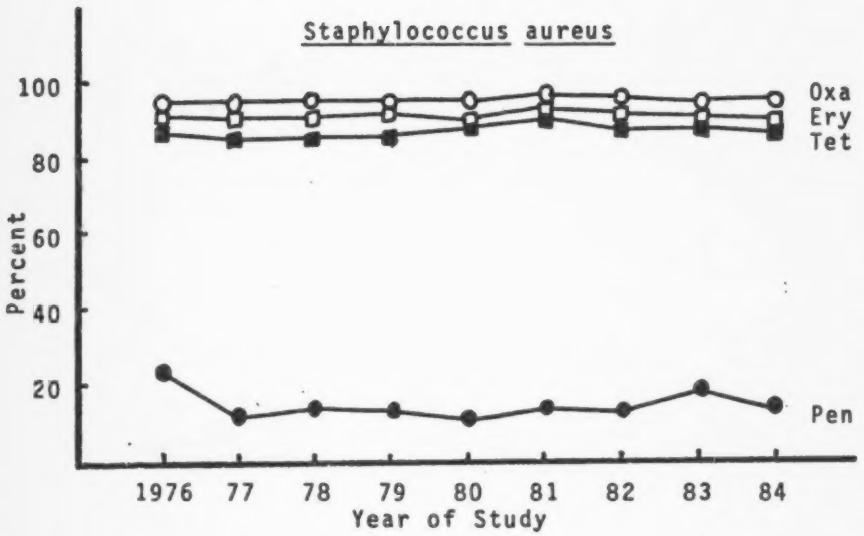
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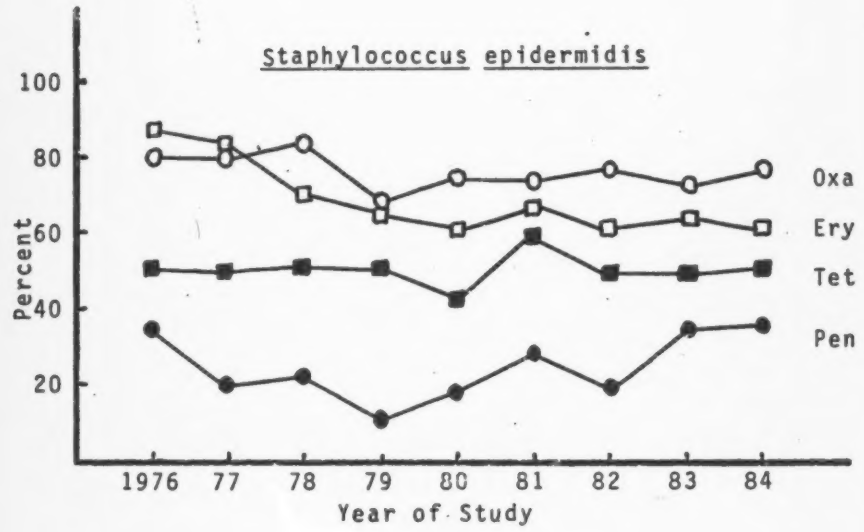
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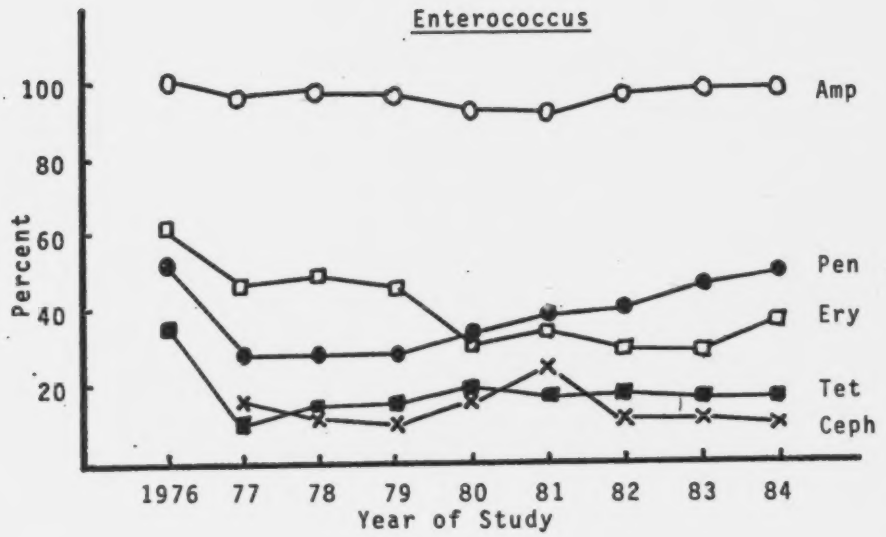
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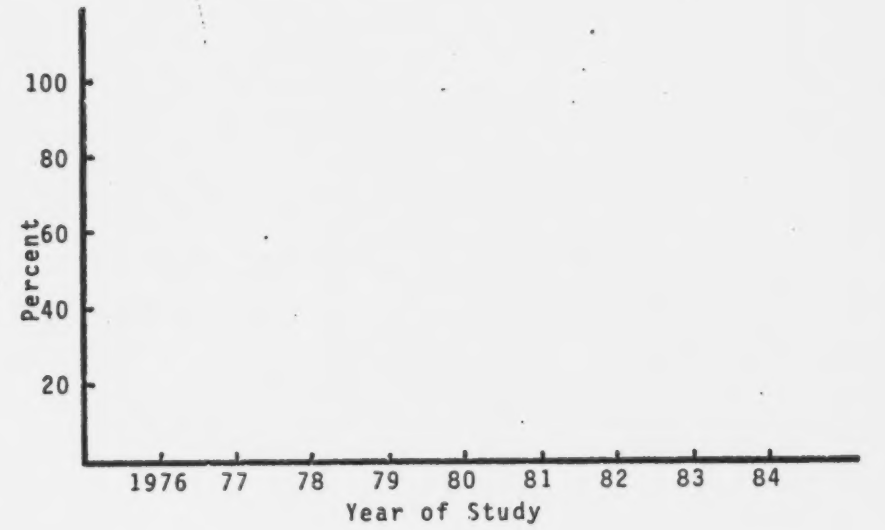
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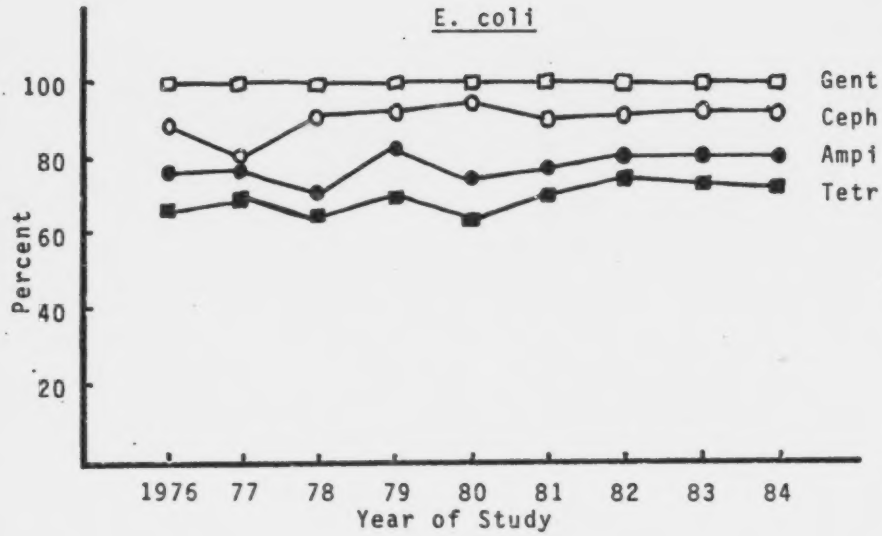
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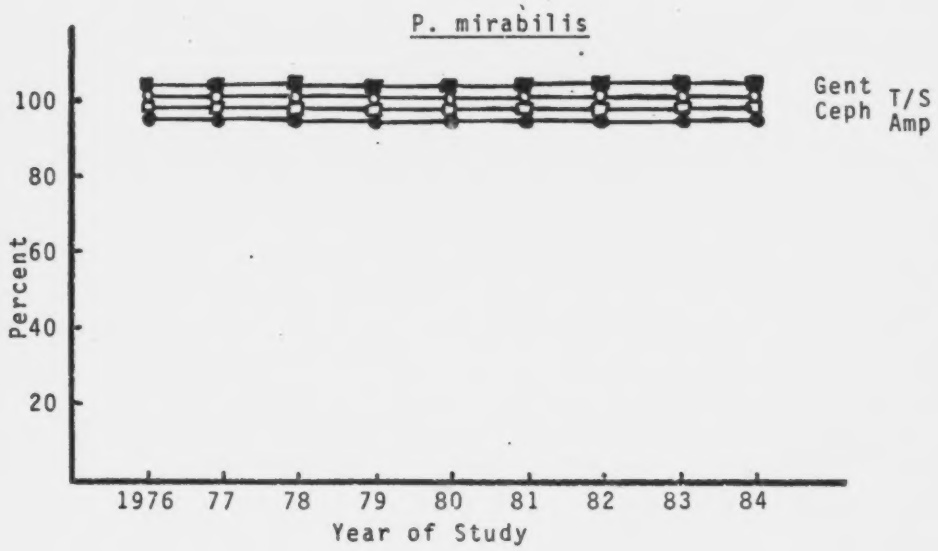
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Antimicrobial Agent Susceptibility Patterns of Bacteria in Hospitals from 1971 to 1982

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Bacterial susceptibility to 16 commonly used antibiotics was analyzed for a 12-year period (from 1971 to 1982, inclusive). Susceptibilities of 5,828,243 strains isolated from a mean of 242 hospitals nationwide and of 194,575 strains isolated at the Massachusetts General Hospital, Boston, Mass., and the Bronx Lebanon Hospital Center, New York, N.Y., were compared. Strains of *Escherichia coli*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* showed virtually the same susceptibilities to antibiotics throughout the 12-year period, whereas *Streptococcus faecalis* and *Staphylococcus epidermidis* showed significant increases in resistance to most antibiotics. The close similarity between antibiotic susceptibilities shown at both the 242 hospitals and the 2 individual hospitals suggests that this analysis accurately reflects trends of bacterial resistance to antibiotics in U.S. hospitals. Since most of the species analyzed produce serious disease and high mortality, their susceptibility to antibiotics is relevant both to physicians treating infectious diseases and to epidemiologists.

Bacterial resistance to penicillin first became evident within a few years of its introduction. Before 1946, 85% of *Staphylococcus aureus* strains were highly susceptible to penicillin; today, only 11% remain susceptible (12). The medical community has been warned repeatedly of major increases in bacterial resistance (23, 28, 34, 39, 41), with many reports citing the increased resistance of *S. aureus* to methicillin (1, 4, 5, 7, 8, 11, 19, 41, 44, 49) and gentamicin (5, 10, 11, 44, 48), of *Haemophilus influenzae* to ampicillin (16, 20, 27, 51), of gram-negative bacilli, especially *Pseudomonas aeruginosa*, to aminoglycosides (13, 17, 24, 31, 32, 37, 38, 50), and the increasing multiple drug resistance among enterococci (30, 33). The new cephalosporins appear to be responsible for bacterial cross-resistance to several beta-lactam antibiotics and occasionally to the aminoglycosides (43).

To assess the magnitude and trends of resistance to the established antibacterial agents (hereafter called antimicrobial agents) in the United States, we analyzed more than 10^7 strains of bacteria. All of these strains had been isolated from hospitals around the country during a 12-year period, and most data were filed on a nationwide computer. This computerized information was compared with that obtained additionally from two hospitals known to have accurate laboratory testing procedures and a well-balanced use of antibiotics in patients, the Massachusetts General Hospital (MGH) in Boston and the Bronx-Lebanon Hospital Center (BLHC) in New York.

MATERIALS AND METHODS

We obtained data on 9,919,999 bacterial strains from Bac-Data Medical Information Systems, Inc. (Clifton, N.J.), a national bacteriological monitoring service for hospital laboratories. From January 1971 to December 1982, Bac-Data collected these laboratory data from 150 to 329 (mean, 242) acute care hospitals of 100 beds or more (in 1982, of the 252 participating hospitals, 96% were accredited by the Joint Commission on Accreditation of Hospitals, and 37% were affiliated with a medical school), which were evenly dispersed throughout the country (2). These subscribing institutions report that bacterial identification was made by conventional methods and that susceptibility testing was done by disk test by the Bauer-Kirby technique (3). Only truly susceptible strains were called susceptible, whereas those with intermediary or equivocal results were labeled resistant so as not to underestimate the levels of resistance. Multiple isolates from the same patient or identical isolates from several patients were not excluded.

Of these nearly 10^7 strains, we analyzed the susceptibilities of the most frequently isolated organisms or those causing the most fatalities (a total of 5,828,243 strains) to 16 commonly used antimicrobial agents. These organisms were: *Escherichia coli*, 1,808,337 strains; *S. aureus*, 989,263 strains; *Staphylococcus epidermidis*, 688,200 strains; *P. aeruginosa*, 499,667 strains; *Streptococcus faecalis*, 563,494 strains; *Klebsiella pneumoniae*, 628,855 strains; *Proteus mirabilis*, 504,291 strains; and *H. influenzae*, 146,136 strains.

We also obtained susceptibility results for the most frequently isolated organisms at MGH over the 10-year period from 1971 to 1981 (six species totaling 171,610 strains), as reported yearly in the MGH laboratory newsletter (A. H. Goroll and A. G. Mulley, ed.), and at BLHC over the 5-year period from 1978 to 1982 (six species totaling 22,965 strains). These data were compared to the nationwide susceptibility results obtained from Bac-Data.

RESULTS

From 1971 to 1982, *E. coli* accounted for 19.2% of all Bac-Data isolated species, immediately followed by *S. aureus* at 10.5% and *S. faecalis* at 6.3%. None of these organisms showed a statistically significant increase in incidence during this 12-year period. The incidence of *S. epidermidis*, on the other hand, rose from 6.2 to 8.5%, *P. aeruginosa* rose from 7.7 to 8.4%, and *H. influenzae* rose from 0.9 to 1.8% during this time, whereas the incidence of *Klebsiella* spp. decreased from 9.1 to 6.7% and *Proteus* sp. decreased from 9.5 to 6%. These accounted for 67.4% of all organisms isolated in the 1982 Bac-Data files.

Results of the 1971 to 1982 annual surveys of the in vitro susceptibilities of these organisms to 16 antibiotics commonly used during this 12-year period are shown in Fig. 1 through 8. Included among the findings were the following.

* Corresponding author.

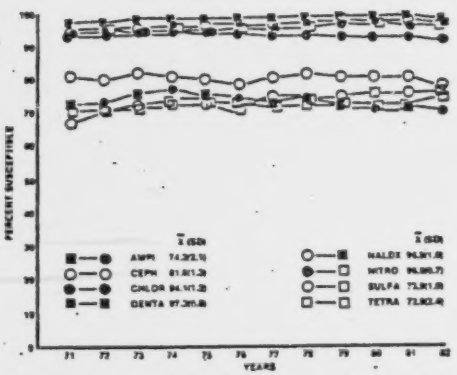

FIG. 1. Percentage of *E. coli* strains susceptible to various antibiotics. Abbreviations: AMPI, ampicillin; CEPH, cephalothin; CHLOR, chloramphenicol; GENTA, gentamicin; NALDX, nalidixic acid; NITRO, nitrofurantoin; SULFA, sulfonamides; TETRA, tetracycline; $\bar{x}$, mean; SD, standard deviation.

E. coli showed no significant change in susceptibility to any of these antibiotics during the 12 years, although there were small increases in its susceptibility to tetracycline, nalidixic acid, and nitrofurantoin (Fig. 1). Likewise, *S. aureus* showed a slight increase in susceptibility to tetracycline, a slight decrease to erythromycin, and a 17% decrease in susceptibility to penicillin; its susceptibility to the other antibiotics, including oxacillin, remained stable. Except for the years 1976 and 1977 when some vancomycin-resistant strains were reported, all strains reported from 1978 to 1982 were susceptible to vancomycin (Fig. 2). *P. mirabilis* continued to remain resistant to tetracycline, and its low susceptibility to nitrofurantoin is decreasing further (Fig. 3). The

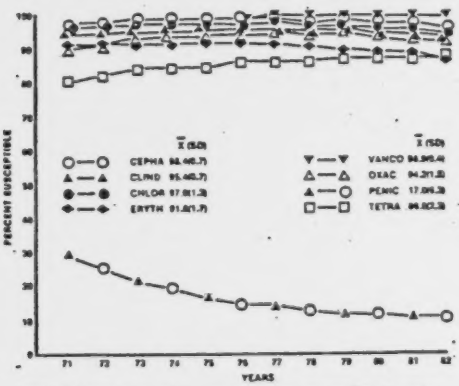

FIG. 2. Percentage of *S. aureus* strains susceptible to various antibiotics. Abbreviations: CEPHA, cephalothin; CLIND, clindamycin; CHLOR, chloramphenicol; ERYTH, erythromycin; VANCO, vancomycin; OXAC, oxacillin; PENIC, penicillin; TETRA, tetracycline; $\bar{x}$, mean; SD, standard deviation.

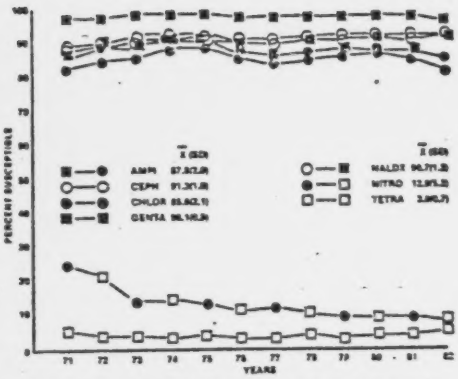

FIG. 3. Percentage of *P. mirabilis* strains susceptible to various antibiotics. For abbreviations, see the legend to Fig. 1.

susceptibility of *H. influenzae* to chloramphenicol and ampicillin remained unchanged (Fig. 4). The susceptibility of *P. aeruginosa* to carbenicillin increased, remained unchanged to colistin, and decreased to gentamicin and tobramycin (Fig. 5). *K. pneumoniae* remained resistant to ampicillin, and its susceptibility remained stable to chloramphenicol and nalidixic acid and increased to tetracycline, cephalothin, and sulfamethoxazole (Fig. 6). Its susceptibility to gentamicin decreased 7% in 1976 and has remained stable since (Fig. 6). *S. epidermidis* has shown a decrease in susceptibility to all antimicrobial agents except tetracycline (Fig. 7). *S. faecalis* showed decreases in susceptibility to cephalothin, chloramphenicol, erythromycin, and penicillin and slight increases to ampicillin, gentamicin, and nitrofurantoin (Fig. 8).

Overall, of 53 Bac-Data analyses of the antibacterial effects of different antimicrobial agents, 8 analyses showed

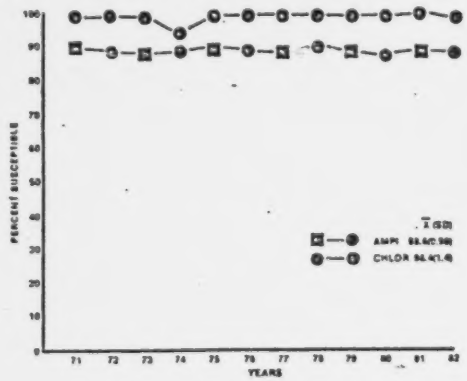

FIG. 4. Percentage of *H. influenzae* strains susceptible to various antibiotics. Abbreviations: AMPI, ampicillin; CHLOR, chloramphenicol; $\bar{x}$, mean; SD, standard deviation.

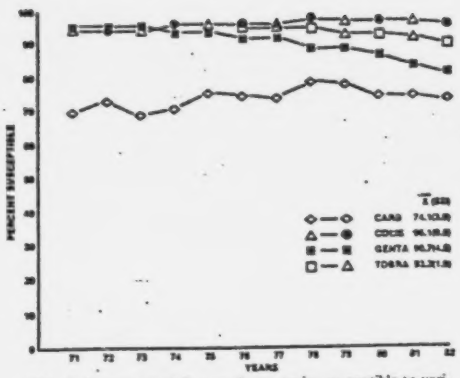

FIG. 5. Percentage of *P. aeruginosa* strains susceptible to various antibiotics. Abbreviations: CARB, carbenicillin; COLIS, colistin; GENTA, gentamicin; TOBRA, tobramycin.

increases in bacterial susceptibility, 16 showed decreases, and 29 showed virtually no change in susceptibility between 1971 and 1982. Moreover, in 25 of the 53 analyses, over 90% of strains remained highly susceptible to the drugs to which they were exposed.

Susceptibility data from MGH and BLHC are shown in Table 1 and are comparable in all respects to those obtained from Bac-Data. During the 10-year period, most species showed only minor variations in their susceptibilities to most antibiotics (notice the small standard deviations). Although MGH showed more strains of *E. coli*, *K. pneumoniae*, and *P. mirabilis* susceptible to ampicillin and carbenicillin and BLHC reported lower susceptibility for these species than Bac-Data, these differences are not statistically significant ($P > 0.5$).

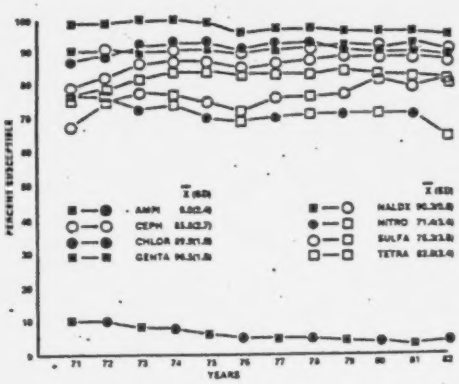

FIG. 6. Percentage of *K. pneumoniae* strains susceptible to various antibiotics. For abbreviations, see the legend to Fig. 1.

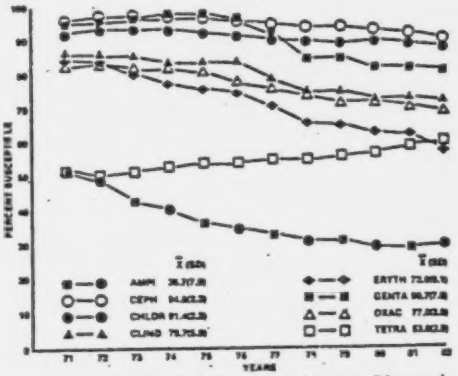

FIG. 7. Percentage of *S. epidermidis* strains susceptible to various antibiotics. Abbreviations: AMPI, ampicillin; CEPH, cephalothin; CHLOR, chloramphenicol; CLIND, clindamycin; ERYTH, erythromycin; GENTA, gentamicin; OXAC, oxacillin; TETRA, tetracycline; $\bar{x}$, mean; SD, standard deviation.

DISCUSSION

The large number of strains tested against various antimicrobial agents (representing 43,246,169 individual tests) minimized possible errors incurred by individual laboratories. The College of American Pathologists showed that the accuracy in 1972 was >90%, and during 1979 to 1981 it was 95.2% (15). This is an indication that susceptibility tests performed in American hospitals, including those reporting susceptibility results to Bac-Data, show a high degree of accuracy. The close similarity between the Bac-Data susceptibility levels and trends and those from the two individual hospitals suggests that the information obtained from Bac-Data accurately represents bacterial susceptibilities to anti-

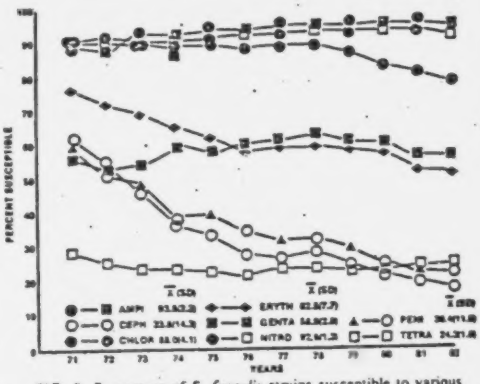

FIG. 8. Percentage of *S. faecalis* strains susceptible to various antibiotics. Abbreviations: AMPI, ampicillin; CEPH, cephalothin; CHLOR, chloramphenicol; ERYTH, erythromycin; GENTA, gentamicin; NITRO, nitrofurantoin; PENI, penicillin G; TETRA, tetracycline; $\bar{x}$, mean; SD, standard deviation.

TABLE 1. Percentage of susceptible strains isolated at MGH and BLHC during the years 1971 to 1981 and 1978 to 1982, respectively

Organism and drug	Mean % of susceptible strains (SD) at following hospital:	
	MGH	BLHC
E. coli		
Ampicillin	77.3 (0.9)	67.8 (1.3)
Cephalothin	83.7 (3.7)	90.0 (1.8)
Chloramphenicol	92.4 (2.8)	94.3 (1.0)
Tetracycline	70.9 (1.5)	75.0 (3.7)
Gentamicin	98.4 (0.5)	99.5 (0.6)
Nalidixic acid	96.8 (1.0)	
Nitrofurantoin	96.0 (0.7)	97.2 (0.6)
Sulfonamides	73.9 (2.4)	71.0 (1.4)
K. pneumoniae		
Ampicillin	9.4 (2.9)	4.0 (2.5)
Cephalothin	86.0 (1.9)	93.4 (2.1)
Chloramphenicol	81.0 (2.3)	93.2 (2.2)
Tetracycline	78.5 (2.8)	89.2 (2.9)
Gentamicin	92.9 (4.7)	97.2 (0.8)
Nalidixic acid		97.2 (2.6)
Nitrofurantoin	76.0 (7.2)	88.4 (3.4)
P. mirabilis		
Ampicillin	94.7 (1.3)	86.0 (5.0)
Cephalothin	97.0 (1.6)	91.6 (3.6)
Chloramphenicol	91.9 (2.5)	91.0 (3.4)
Tetracycline		3.8 (1.6)
Gentamicin	98.4 (0.8)	99.2 (0.8)
Nalidixic acid		96.2 (2.6)
Nitrofurantoin	3.9 (2.6)	11.2 (6.1)
P. aeruginosa		
Carbenicillin	80.7 (3.5)	78.0 (3.3)
Gentamicin	87.8 (7.4)	85.4 (5.7)
Tobramycin	95.0 (3.4)	95.4 (3.3)
Colistin	98.4 (1.1)	
S. aureus		
Oxacillin	97.0 (3.3)	96.8 (1.3)
Penicillin G	15.3 (3.8)	4.5 (1.9)
Cephalothin	98.4 (1.9)	94.4 (0.9)
Erythromycin	88.7 (5.3)	91.2 (1.9)
Clindamycin	93.1 (5.7)	97.4 (1.1)
Chloramphenicol	94.9 (3.2)	97.0 (1.2)
Tetracycline	90.1 (2.3)	89.2 (6.2)
S. faecalis		
Ampicillin		95.4 (1.1)
Penicillin G	27.9 (6.0)	42.6 (24.8)
Cephalothin	20.1 (8.9)	25.6 (12.5)
Erythromycin	56.9 (13.2)	74.2 (6.2)
Chloramphenicol	77.4 (2.1)	86.8 (5.1)
Gentamicin		78.4 (9.0)
Tetracycline	19.4 (2.8)	24.0 (9.2)
Nitrofurantoin	94.9 (1.5)	

biotics in U.S. hospitals. However, it should be noted that we have included Bauer-Kirby intermediate zone sizes as resistant so as not to understate resistance prevalence. This could result in a slight overestimate of resistance in some cases, although this should not interfere with the validity of our conclusions concerning national trends. Since infections with most of the species analyzed result in serious illness with high mortality (*S. aureus* [9, 42], *E. coli* [14, 21, 29], *P. aeruginosa* [6, 46], and *S. faecalis* [25, 45]), the susceptibility data reported above are highly relevant both to physicians treating infectious diseases and to epidemiologists.

The appearance of ampicillin resistance in *H. influenzae* 1 to 3 years before the recognized identification of plasmid-borne ampicillin resistance should be discussed. The Bac-Data figures are based on Bauer-Kirby tests, and we have chosen to err on the side of resistance by including isolates showing intermediate zone sizes as resistant. Thus, the ca. 10% regarded as resistant includes isolates originally classified as intermediate. It is now recognized that ampicillin resistance in *H. influenzae* as measured by diffusion tests may yield a certain percentage of false-positive results. It is also possible that clear-cut plasmid-mediated resistance did exist before its recognition in 1974, and the frequency of reported ampicillin therapeutic failures with *H. influenzae* in the early 70s does little to dissuade us of that possibility. The levels of vancomycin resistance in *S. aureus* in 1976 and 1977 could also result from disk intermediate zones in those years that Bac-Data records were first kept for this agent. Although the 6% *Haemophilus* resistance to chloramphenicol obtained from Bac-Data in 1974 was not noted in the literature during that and the following year, three reports of chloramphenicol resistance were published during 1976 (19, 22, 26), and one appeared in 1978 (18).

It has been reported that bacterial resistance to antimicrobial agents is increasing worldwide, the United States included (35, 36). In contrast, a study conducted in Switzerland concluded that bacterial resistance to antimicrobial agents in that country has not changed during the years 1974 to 1979 (47), and one of us (2) reached the same conclusion for the years 1973 to 1977 for a large group of hospitals in the United States. Many of the resistance reports are based on surveys conducted in a single institution, in which resistance may be a consequence of unbalanced antibiotic usage or due to a high rate of nosocomial infections (1, 11, 17, 19, 31). Some reports of bacterial resistance are supported by very limited evidence; for example, one series discusses only 28 strains of *H. influenzae* resistant to ampicillin from a total of 256 strains analyzed (16, 20, 27, 51). Two of these four publications actually report a single resistant strain each (16, 27). Since 1971, 6,383 papers on bacterial resistance have been published in the English language alone. Indeed, the very abundance of literature on this subject contributes to the perception that bacterial resistance to antimicrobial agents is growing at an alarming pace. It is understandable that many of us judge antimicrobial agent profiles of bacteria by limited observations in large tertiary-type institutions of our own or of our colleagues. As one would expect, it is precisely in that setting that the selective pressure for resistance is at its peak. In addition, it is the organism with the exceptional antibiogram that remains uppermost in the minds of the observers and leads to the conclusion that antimicrobial susceptibility is undergoing dramatic changes.

Although our study confirmed that *S. faecalis* (which is naturally resistant to many antibiotics) and *S. epidermidis* (which in most cases remains a colonizing organism) have developed additional resistance to antibiotics, the other species analyzed showed little change in antimicrobial agent susceptibility during the last 12 years. Although local outbreaks of bacterial resistance do arise and many have serious consequences, bacterial susceptibility on a national scale has remained virtually unchanged during the last decade. This may, perhaps, be credited to the continuous effort in U.S. hospitals to achieve balanced usage of antibiotics.

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Mr. GORE. One final question to all three of you, just briefly. What would you recommend be done about this problem? Dr. Levy, you've thought a lot about it. What would—what would your recommendations be?

Dr. LEVY. I hope it was obvious from my brief summary that the approach and the use of antibiotics in every area should be reconsidered, and that these drugs should be more thoughtfully utilized.

I think what the organization of which I am also part, the Alliance for the Prudent Use of Antibiotics, is trying to do is to educate, educate not just those people using them and dispensing them, but everyone, so that the attitude toward them will be much more prudent than it is now. And I think that, from a general standpoint, the education process—that is, at the medical school level, the nursing level, and in the schools—and I've done some of that myself in local high schools—is important. So that right from the start, individuals are not giving out these drugs, asking—asking for that drug. That's No. 1.

And No. 2, I think that it has to be looked at from an international standpoint, because what goes on in other countries is very important to what's going to come here, for the many reasons that I've described.

Mr. GORE. Very good.

Dr. Hughes.

Dr. HUGHES. Well, I would certainly agree with Dr. Levy that the education of physicians is terribly important, because I—I do feel that antibiotic usage does—does relate to patterns of antibiotic resistance.

I think also there probably is a need for some more evaluation of some of the other alternative strategies to influencing antibiotic usage that I suspect we're going to hear about from the next panel.

Mr. GORE. Very good.

Dr. Parry?

Dr. PARRY. I think you have to divide the approach into two areas. One is outpatient use and the other is inpatient use. I think outpatient use has to be controlled by education and, as Dr. Levy mentioned, education of both physician and patient. As far as inpatient antibiotic use is concerned—and I think clearly the level is high raising concerns about resistance problems—that also is an educational approach.

But, in addition, I'm not so sure that within the hospital environment, there shouldn't be more controls placed on actual prescribing

patterns. And this is already being done in many, many institutions where there are infectious disease specialists, or hospital epidemiologists, or active pharmacy and therapeutic committees, where there are actual controls placed on the use of drugs, both in dosage, type, restrictions by diagnosis and by—by other factors. I think this needs to be done in the hospital environment. I don't think it can be done very well in the outpatient environment.

Mr. GORE. OK. Well, thank you, all three for——

Mr. VOLKMER. Mr. Chairman. Mr. Chairman.

Mr. GORE. Yes.

Mr. VOLKMER. I just ask the gentleman a question. Dr. Levy, the Alliance for Prudent Use of Antibiotics, how long has it been in the—in the——

Dr. LEVY. It was established at the end—established the end of 1981 as a response to a statement issued in that same year from 30 different members of—clinicians and basic scientists from 30 different countries. And the response from scientists all over the world caused the creation of this group, which is international, members of 60 countries. It is purely an educational one. And it is really called the Alliance because it's bringing together individuals and groups in different countries who are being asked to look at the problem in their own local context. It's never been considered that one country's going to be able to tell another how to deal with the problem. But as long as we can let them know that the problem exists and increase awareness, which is, I think, what happened, then I think that at the individual local level these questions can be answered and worked on. And I'm happy to say that that is what's happening.

Mr. VOLKMER. In other words—if I may, Mr. Chairman, just briefly—if we would do—have a prudent use of antibiotics in this country and we see some of the resistance factors—resistance decrease and susceptibility increase, and yet it wasn't done, let's say, in Canada, and then they—there their resistance created in bacteria and then somebody comes down and visits and then I get it, and then the doctor thinks I got what, you know, the next door neighbor had yesterday, I may be surprised, huh?

Dr. LEVY. I think we expect that all the time. We always ask, where have you been recently? And I think that that is one of the other reasons to know from every country what is resistant in your country today or yesterday. And that kind of information is not available. It's generally several years late. And I think having individuals and groups working on it individually so that a telephone notice or what-all, we would have that data available, and we would hope to have it for physicians all over the world. This would be ideal.

Mr. VOLKMER. What—what I'm trying to say is we're not isolated any longer in the world, and what we do here isn't going to necessarily control everything that's going to occur.

Dr. LEVY. That—that is correct. But I think that we, like other countries, have got to take stock of our usage because we have our own problems right here.

Mr. GORE. Counsel for the minority have questions?

Mr. LAMINA. Thank you, Mr. Chairman. I have to be going, but it occurred to me last evening, and I'm sure that a few people in the

audience are aware, that—I believe today's your final hearing as chairman of the subcommittee. And I just wanted to say that, while I can only comment for Congressman Skeen and myself, I'm sure other minority members would agree that, under your leadership, this subcommittee has laid the groundwork for a lot of important legislation and probably much needed change, and we just all appreciate it.

Mr. GORE. I appreciate that. Thank you very much. I've enjoyed working with you and with all of the minority staff and minority members, and I hope you have a good Christmas.

We're going to—we're going to continue with one more panel before we close it down for the year. I'd like to thank this panel very much. Thank you and keep up the good work. I appreciate your presence here today.

Our final panel of today and of the year is Dr. William Schaffner, infectious disease specialist in the department of preventive medicine at Vanderbilt and—in Nashville; and Dr. Edward Kass, director of the Channing Laboratory at Harvard Medical School in Boston; Dr. Sidney Wolfe, director of Public Citizen Health Research Group here in Washington; and Joseph Stetler, president of the Pharmaceutical Manufacturers Association, accompanied by Dr. John Jennings, vice president for science and technology with the PMA.

If all of you would come up to the witness table, we'll—we'll crank it up.

Joe Stetler, are you still president? I saw a news story saying that somebody else had been elected. Has that taken effect yet?

Mr. STETLER. January 22.

Mr. GORE. January 22. Well, when there is a crisis at the PMA in times of turmoil or transition or whatever, they always go to the person who can handle the job. We're delighted.

Mr. STETLER. I hope your confidence is not misplaced.

Mr. GORE. This panel has a number of close friends, close personal friends, on it. Delighted to—to have Dr. Wolfe here. And Dr. Bill Schaffner is a personal friend going way back. Indeed, we used to be neighbors down on Granny White Pike in Nashville, TN.

Mr. STETLER. Sure enough. Sure enough.

Mr. GORE. We're delighted to have all four of—all five of you here. Without objection, your prepared statements will be placed in the record at this point. If you care to summarize any of your statements, please feel free to do so. We'll begin with you, Dr. Schaffner. Welcome, and pull that microphone close enough so we can hear you, and please proceed.

STATEMENTS OF WILLIAM SCHAFFNER, M.D., INFECTIOUS DISEASE SPECIALIST, DEPARTMENT OF PREVENTIVE MEDICINE, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE, NASHVILLE, TN; EDWARD H. KASS, M.D., DIRECTOR, CHANNING LABORATORY, HARVARD MEDICAL SCHOOL, BOSTON, MA; SIDNEY WOLFE, M.D., DIRECTOR, PUBLIC CITIZEN HEALTH RESEARCH GROUP, WASHINGTON, DC; AND C. JOSEPH STETLER, PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, WASHINGTON, DC; ACCOMPANIED BY JOHN JENNINGS, M.D., VICE PRESIDENT FOR SCIENCE AND TECHNOLOGY, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, WASHINGTON, DC

[The biographical sketch of Dr. Schaffner follows:]

Biographical Sketch

Name: William Schaffner, M.D.

Present Position: Chairman, Department of Preventive Medicine
Chief, Division of Infectious Diseases,
Department of Medicine, Vanderbilt University
School of Medicine, Nashville, Tennessee

Degrees: Yale University, B.S., 1957
Cornell University Medical College, M.D., 1962

Internship and Residencies: Vanderbilt University Hospital, 1962-1964,
1968-1969

Fellowship in Infectious Diseases: Vanderbilt University School of Medicine,
1964-1966

Selective Service: Epidemic Intelligence Service Officer of the National
Communicable Disease Center (now the Centers
for Disease Control), USPHS., 1966-1968

Board Certification: Internal Medicine, Infectious Diseases, and
Preventive Medicine

Dr. Schaffner is a member of numerous professional societies, is a consultant to the Tenneessee Department of Public Health, the Centers for Disease Control, the American Hospital Association, and the World Health Organization. He is the author or co-author of over 130 publications in the medical literature.

Dr. Schaffner's main research interests include studies of prescribing practices, the occurrence of communicable diseases in the community, hospital-acquired infections, and aspects of clinical infectious diseases.

Dr. SCHAFFNER. Thank you, Mr. Chairman, Mr. Volkmer, members of the committee and colleagues in the audience.

Numerous surveys have indicated that antibiotics are among the most frequently prescribed drugs in this country. Antibiotics remain extraordinarily effective in treating many bacterial infections. However, physicians have become increasingly aware that there are complications associated with their use. And these include allergic reactions, drug toxicities and, as we've heard this morning and you've heard yesterday, problems with bacterial resistance. So the original wonder drugs continue to give us cause to marvel; their use also has provided us with problems to ponder.

Considerable effort recently has been directed to reviewing and controlling the use of antibiotics within hospitals. And this activity is appropriate, but it should be remembered that most prescriptions for antibiotics are written in physicians' offices and in outpatient settings. In addition, although the emergence of antibiotic resistance often is considered primarily in the context of the hospitalized patient, several bacterial species have developed resistance to antibiotics in the community, away from the hospital environment, and I've provided you a list of them.

It's clear that a need exists for educational programs regarding appropriate use of antibiotics in office practice. To be effective, however, we believe programs cannot be designed from the armchair. It's important first to determine who is pre—prescribing what antibiotics to whom and for which diagnoses. Only then, based on these documented prescribing habits, can educational programs be designed specifically for those groups of physicians who have been identified as poor prescribers. Also, after the educational program has been completed, continuing surveillance of prescribing practices can be used to evaluate the effects of the program. We can give ourselves a report card—did we do any good?

Because only very little was known concerning the prescribing habits of physicians in office practice, a research team at the Vanderbilt University School of Medicine undertook a series of studies in this area. The populations studied were particularly germane to the House of Representatives here because they were Medicaid recipients, recipients of government-sponsored medical care in the State of Tennessee, and the physicians who provided medical care under the auspices of that program. And this includes approximately 400,000 eligible persons, almost 10 percent of the State's population, and over 5,000 physicians who provided services to these populations. So these are populations of considerable size. Data collected for the normal administrative and fiscal purposes of Medicaid were used, as well as information in the State's public directory of licensed physicians.

It's important to note that during the conduct of these investigations, meticulous constraints were in place to protect the confidentiality of patients and physicians.

The prescribing of two antibiotics was carefully studied. Both are, for all practical purposes, contraindicated in office practice. They're associated with the risks of serious toxic effects, side effects, which are thought to be inappropriate for their use in the treatment of the relatively minor infections that one generally treats in outpatient settings. The drugs were chloramphenicol,

which is an antibiotic which is very effective but is associated with rare aplastic anemia, which is an inability of the human bone marrow to produce white blood cells and red blood cells; and tetracycline, which is also an effective drug, but in young children, children under the age of eight, it produces the staining of teeth, such in—such as in that little girl, that dark staining of the front teeth. The constraints against the use of these drugs appear in standard texts, are emphasized in the drugs' package inserts, and should be widely known.

The first study, the chloramphenicol review, was conducted some time ago, in 1973–74, when we first began our investigations. And what we discovered was that, as you see in the line—the column to the left, the overall prescribing rate of physicians was only 6 percent, and we thought that this was very laudible. However, when we looked at the use of tetracycline being given to young children, we discovered that 27 percent of doctors treating these young children gave them tetracycline. It seemed then to us that the cautions regarding the use of chloramphenicol were widely known and observed. However, the contraindications regarding the use of tetracycline in young children either were not known or were ignored—thought not to be important.

Now we analyzed the prescribing practices further, and to make a somewhat long study—story short, we discovered that the kind—the type of specialty practice influenced prescribing practices as well as relative rurality of location. The more rural the location of practice, the more apt the physician was to misuse these antibiotics. And we—when we looked at rural family practitioners, we discovered that, in contrast to the low 6-percent overall prescribing rate of chloramphenicol, 21 percent of rural family practitioners used this drug; and, likewise, when we looked at the use of tetracycline in young children, 52 percent of rural family practitioners used this drug. So we clearly had defined a group of physicians who needed some more information, who needed to bring—be brought up to date.

And, indeed, when we looked further, we discovered that there were 20 doctors who wrote half the prescriptions for virtually half of the recipients, a virtual handful. And likewise with tetracycline being given to young children, 26 physicians wrote 54 percent of the prescriptions to almost half of the recipients. If we could but reach out and touch them with information, perhaps we could eliminate virtually half the problem, at least in the Medicaid Program, a very exciting prospect.

To emphasize the point further that you have to know who was prescribing what for whom, we noted that the tetracycline study also revealed that after family practitioners, internists and surgeons prescribed more tetracycline to young children in office practice than did other specialists, including pediatricians whose record was excellent. Now this relatively high ranking of surgeons and internists was a distinctly unexpected result. It's doubtful that any of the eminences testifying today would have predicted that internists and surgeons might require remedial education in the use of antibiotics for the treatment of children. Such surprises reinforce the need for documentation of actual prescribing practices in order to direct effective educational programs. We would never have direct-

ed an educational program at internists and surgeons for prescribing antibiotics to children under the age of 8.

Now, as a consequence of these and a number of other studies, we have initiated a physician education program. It began in 1980, and it was a controlled trial of three educational methods to improve antibiotic prescribing in office practice in our State. This venture was supported by a grant from the National Center for Health Services Research, and the major findings of the study are detailed in the references which I have given you. But let me describe it very briefly.

The program, first—the program—whoops, yeah, I told you that already. The program in prescribing improvement was sponsored by the physician's organizations, the professional organizations, in the State of Tennessee, and it became an official program of the Tennessee Medical Association in collaboration with all of the other professional societies on that slide. The work was performed in collaboration with the team at Vanderbilt.

Four antibiotics were selected as the subjects for separate educational interventions: chloramphenicol and tetracycline, which I've mentioned; a drug called clindamycin, which at that time was associated, and still is, with the development of a certain kind of colitis. Those three drugs are thought to be contraindicated for use in office practice because they're just too toxic. They're very effective, useful in hospital practice in many instances, but too toxic for use in office practice. And in contrast to them, a group of orally administered drugs called the cephalosporins, which are very effective, very safe, but often much more expensive than alternative drugs.

The rationale, therefore, was to present two kinds of messages to physicians. One, quality of care issues, these drugs are too—too risky to use; and issues of costs of care, these drugs are too expensive. We were curious as to which message physicians would be more likely to respond to.

Three educational techniques were tested for each of these drugs: First, a special designed mail brochure; second, doctors were visited in their offices by a trained drug educator, a pharmacist; and three, doctors were visited in their offices by other physicians who were specially trained whom we call physician counselors.

The brochures were written by us, approved by the advisory committee, they were produced professionally, and they were written clearly and simply and they addressed the issues of treating infections in office practice in a very practical fashion.

The drug educator was a recent pharmacy graduate who was very qualified, poised and articulate, we thought was an effective teacher, and was modeled after a continuing educational device of proven effectiveness, the pharmaceutical sales representatives, the detail persons with whom we're all familiar. They're very effective. The drug educator made appointments with doctors, was introduced as representing the Tennessee Medical Association, and had brief discussions, usually less than 15 minutes, with doctors about the use of the antibiotics in question. Only a single antibiotic was the subject of each visit. And at the conclusion of the interview, the visited doctor was given a copy of the relevant brochure.

The physician counselors were recruited by members of the advisory committee, were senior members of the medical community in

part-time practice, and both the physician counselors and the drug educator were given special training in interviewing techniques, as well as technical training in the various antibiotics in question. The types of visits that the two made were entirely similar.

Now, doctors to be visited were chosen on the basis of their recorded prior Medicaid prescribing experience. We used the targeting concept. Only doctors who had used the antibiotics in question during the previous year were targeted for educational interventions. These doctors were sorted into four groups: those who received a brochure, those who were visited by the drug educator, a control group so we could see what happened to prescribing practices without any educational intervention, and a group visited by the physician counselors. And they were separated in different areas of the State for logistic convenience. The prescribing practices throughout the State were entirely similar.

Two assessments of the program were made. First, we wanted to know whether our visitors would be received well by physicians. When we started this program, there was some concern that these folks who went into doctors' offices trying to change prescribing practices would not be warmly received. So we made several assessments of receptivity. And second, the prescribing of the drugs in question—and obviously this is most important—during the year after the educational program was compared with the physician's use of the drug during the year before the program.

So let's go to the results. First, the drug educator and the physician counselors were well received by the visited doctors in their offices. Tennessee physicians are courteous, warm and receptive. Over 85 percent of the scheduled visits could be completed. Ninety-five percent of those visits were assessed by the person going into the office as friendly. And then the doctors were called within a month by someone else from the TMA, from the Tennessee Medical Association, and they were said—they were asked, do you remember that visit? Do you think it was any good? And we figured this was an opportunity for physicians to blow off steam and tell the TMA that they were wasting their dues money and the like. But 85 percent of the doctors said that the visit was useful, they liked that this—this was an activity of their professional society. They felt that they were getting unbiased, straight information for which they were grateful, and they even began making suggestions for topics for future visits.

Lesson one, doctors are receptive, they want more information, and they want it delivered in a practical, useful fashion.

Mr. GORE. So you had a 15-percent resistance level? [Laughter.]

Dr. SCHAFFNER. Perhaps it was just too busy. I'm not even willing to say that they were resistant. Some of those waiting rooms were very full.

Mr. GORE. At a minimum, you had a 6-percent resistance level.

Dr. SCHAFFNER. Yeah, that's right.

Mr. VOLKMER. I—what it tells me is that people in Tennessee are just very friendly. [Laughter.]

Dr. SCHAFFNER. I would agree with that. I can't argue with that. [Laughter.]

Now, let's look at our three—our three educational techniques. First of all, the single mailed brochure, even though it came in the

envelope of the—the very distinctive envelope and paper stock of the Tennessee Medical Association, had no measurable effect on prescribing practices. One piece of mail won't do it. This, despite the care taken to make the brochure useful and attractive.

Second, the—do I have a slide there? Yeah. Second, the drug educator was only modestly successful. Although resembling a pharmaceutical sales representative, the drug educator made only one brief visit to each doctor on each antibiotic topic. And although this had a modest beneficial effect in improving prescribing practices, it was less, frankly, than we had hoped for. It should be noted that a pharmaceutical sales representative depends upon establishing a continuing personal relationship with doctors in order to successfully promote their company's products. This study could not determine whether multiple visits by a drug educator could redirect prescribing practices.

But I would direct your attention to a concurrent study done also under the auspices of the National Center for Health Services Research by Doctors Avorn and Soumerai, and I've given that reference here, our colleagues in Boston, who have demonstrated at least two educational visits by specially trained pharmacists can have a beneficial effect on prescribing practices. And one of the drugs that they studied was an antibiotic, Cephalexin, the oral cephalosporin which is entirely similar to the project that we've done here. So they've had a little bit better luck in—in their use of—of this method.

Now in contrast to that in our study, the brief visits by the physician counselors were remarkably successful in reducing the prescribing of both the contraindicated antibiotics and the oral cephalosporins during only a single visit. For the contraindicated antibiotics, the reduction in prescribing which could be attributed to the physician counselor visits was 34 percent in the average number of prescriptions written per doctor. Also, the proportion of doctors prescribing these medications at all was reduced by 18 percent, and the average number of prescriptions written per doctor during the year was reduced by approximately half.

When considering the oral cephalosporins—this is the cost effectiveness part of the—part of the study—the physician counselors again produced a strong attributable reduction in the number of patients receiving these drugs per doctor—a reduction of 21 percent—and in the average number of prescriptions written per doctor during the year—again, a reduction, coincidentally, of 21 percent. These prescribing reductions lasted throughout the initial year of evaluation. That's a long time. We were so intrigued with this that we, on our own, studied it for another year. This beneficial effect of the physician counselors persisted through a second year after the single 15-minute educational intervention. This is a striking result.

We conclude that doctors in practice are eager for information which is presented in an unbiased and helpful fashion, and which will aid them in the appropriate use of antibiotics. In our study, the messenger was more important than the message. Doctors, when visit—when visited in their offices by a physician counselor, responded equally well to the message of improved patient care, as well as to the message of reducing excessive costs. And when they

get the message and change their behavior, the effect lasts a long time. Indeed—if you will indulge my hyperbole—I am unaware of any other brief educational encounter on any subject that has ever been shown to be as effective in changing anyone's behavior as was this 15-minute visit of a doctor in practice by physician counselors representing their professional organization.

The study demonstrates that a nonpunitive educational program sponsored by the medical profession can change practice—patterns of office practice that are inappropriate or excessively costly. It's clear that medical practice can be changed by a variety of means—regulation, reimbursement and sanctions. And undoubtedly, they are also effective, these methods have obvious disadvantages. The success of the educational interventions conducted in Tennessee and by Doctors Avorn and Soumerai are a challenge to the medical profession and to all parties interested in delivering effective and appropriate medical care. The potential for improving prescribing practices of antibiotics and numerous other drugs by the use of similar educational programs, we think, is an exciting one.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Schaffner follows:]

TESTIMONY OF

WILLIAM SCHAFFNER, M.D.

Chairman, Department of Preventive Medicine

and

Chief, Division of Infectious Diseases, Department of Medicine

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Subcommittee on Investigations and Oversight of the Science and Technology Committee, U. S. House of Representatives

December 19, 1984

Numerous surveys have indicated that antibiotics are among the most frequently prescribed drugs in this country. Antibiotics remain extraordinarily effective in treating many bacterial infections. However, physicians have become increasingly aware that there are complications associated with antibiotic use. These include allergic reactions, drug toxicities, complicating superinfections and especially the emergence of bacterial strains which are resistant to one or more antibiotics. Although the original wonder drugs continue to give us cause to marvel, their use also has provided us with problems to ponder.

Considerable effort recently has been directed to reviewing and controlling the use of antibiotics within hospitals. This activity is appropriate, but it should be remembered that most prescriptions for antibiotics are written in physicians' offices and in out-patient settings. In addition, although the emergence of antibiotic resistance often is considered primarily in the context of the hospitalized patient, several bacterial species have developed resistance to antibiotics in the community, away from the hospital environment (see Table 1).

Table 1
Examples of Bacterial Pathogens that Have Developed Antibiotic Resistance outside of the Hospital Environment

Bacterial Pathogens	Type of Infection	Antibiotic
Group A streptococci	strep throat	Tetracycline, erythromycin
Meningococci	meningitis bloodstream infection	Sulfonamide
Pneumococci	pneumonia meningitis	Penicillin, tetracycline, others
Gonococci	gonorrhea	Penicillin, tetracycline, spectinomycin
Shigella	diarrhea	Multiple antibiotics
Salmonella	diarrhea bloodstream infection	Multiple antibiotics
Hemophilus influenzae	meningitis bloodstream infection	Ampicillin, chloramphenicol

It is clear then that a need exists for educational programs regarding appropriate use of antibiotics in office practice. To be effective however, programs cannot be designed from the armchair. It is important first to determine who is prescribing what antibiotics to whom and for which diagnoses. Only then, based on these documented prescribing habits, can educational programs be designed specifically for those groups of physicians who have been identified as poor prescribers. Also, after the educational program has been completed, continuing surveillance of prescribing practices can be used to evaluate the effects of the program.

Background and Methods. Because little was known concerning the prescribing habits of physicians in office (ambulatory care) practice a research team at the Vanderbilt University School of Medicine (including the author and Wayne A. Ray, Ph.D. and Charles F. Federspiel, Ph.D.) undertook a series of studies in this area. The populations studied were the Medicaid recipients in the state of Tennessee and the physicians who provided medical care under the auspices of that program. This includes approximately 400,000 persons who are eligible for the Tennessee Medicaid Program (almost 10% of the state's population) and over 5,000 physicians who provide services to this population. Data collected for the normal administrative and fiscal purposes of Medicaid were used, as well as information in the state's directory of licensed physicians.

It is important to note that stringent efforts were made to protect the confidentiality of both patients and physicians. Individuals were identified only by number in the computer record; names were not used. Furthermore, the Vanderbilt Committee for the Protection of Human Subjects reviewed and approved the study protocols.

The prescribing of two antibiotics was carefully studied; both are contraindicated in office practice. Both antibiotics are associated with risks of serious toxic effects and are thought to be inappropriate for office practice where the infections encountered are usually minor. Other less hazardous, equally efficacious antibiotics are available. The two drugs were: chloramphenicol (in patients of all ages) and tetracycline (to children less than 8 years of age). Chloramphenicol is associated with the rare occurrence of aplastic anemia (failure of the bone marrow to produce white blood cells and red blood cells); the use of

tetracycline in young children often results in staining of the teeth. The constraints against the use of these drugs appear in standard texts, are emphasized in the drugs' package inserts, and should be widely known.

The chloramphenicol review (conducted in 1973-74) (Reference 1) discovered that only 6% of physicians who participated in the Medicaid program prescribed chloramphenicol. In contrast, the tetracycline study (conducted between 1973-75) (Reference 2) revealed that over one-fourth (27%) of doctors treating young children gave them tetracycline. It seemed that the cautions regarding chloramphenicol were widely known and observed however, the contraindications regarding the use of tetracycline in young children either were not widely known or were not believed.

Further analysis correlated the prescribing of these antibiotics with medical speciality and location of practice. A similar pattern of prescribing for both drugs was revealed. Both the specialty of family practice and rural location of practice were independently associated with increased rates of prescribing of both chloramphenicol and tetracycline in office practice. Of rural family practitioners, 21% used chloramphenicol (in striking contrast to the low 6% overall rate), and 52% prescribed tetracycline (double the 27% overall rate). Furthermore, it was shown that a relatively small number of physicians were responsible for a large proportion of the prescriptions written. Only 20 doctors wrote 55% of the chloramphenicol prescriptions to 47% of the recipients. Likewise, only 26 doctors wrote 54% of the tetracycline prescriptions to 45% of the young children who were given this antibiotic. Thus, analysis of prescribing patterns was able to define special physician target groups that clearly required educational efforts to improve their prescribing practices.

To emphasize this point further, the tetracycline study also revealed that after family practitioners, internists and surgeons prescribed more tetracycline to young children in office practice than did other specialists (including pediatricians). This was a distinctly unexpected result; it is doubtful that anyone would have predicted that internists and surgeons might require remedial education in the use of antibiotics for the treatment of children. Such "surprises" reinforce the need for documentation of actual prescribing practices in order to design effective educational programs.

The Physician Education Program. Beginning in 1980, a major controlled trial of three educational methods to improve antibiotic prescribing in office practice was undertaken in Tennessee. This venture was supported by a grant from the National Center for Health Services Research. The major findings of the study will be briefly summarized here; details are available in References 4 and 5.

The "Program in Prescribing Improvement" was sponsored by the Tennessee Medical Association in cooperation with the Tennessee Society of Internal Medicine, the Tennessee Academy of Family Physicians, the Tennessee Chapter of the American Academy of Pediatrics, and the Tennessee Department of Public Health. The work was performed in cooperation with the investigators from the Vanderbilt University School of Medicine.

Four antibiotics were selected as the subjects for separate educational interventions: chloramphenicol, tetracycline (to children less than 8 years of age), clindamycin, and the group of orally-administered cephalosporin drugs. The first three antibiotics are

contraindicated for the treatment of minor infections in office practice because of their risk of serious toxicity (clindamycin is associated with the development of a type of colitis). The rationale for choosing these drugs was to improve the quality of medical care delivered to the patient. In contrast, the oral cephalosporin antibiotics are both safe and effective drugs. The rationale against their widespread use is cost; they are many times more expensive than alternative, effective antibiotics for the treatment of many infections. Thus, using these two different rationales, it was possible to compare physician responses to the two issues of: 1) quality of care; and 2) costs of care.

Three educational techniques were tested: 1) a specially-designed mail brochure, 2) visits to doctors by a trained drug educator, and 3) visits to doctors by specially recruited and trained physician-counselors.

The brochures were written by the investigators and approved by an advisory committee established by the sponsoring professional organizations. They were written clearly and simply; they addressed the issues of treating infections in office practice in a practical fashion.

The drug educator was a recent pharmacy graduate who was poised, articulate and who was judged to be an effective teacher. This intervention was modeled after an existing educational device of known effectiveness - namely, the pharmaceutical sales representative. The drug educator made appointments with doctors, was introduced as representing the Tenessee Medical Association and had brief discussions (usually no longer than 15 minutes) with doctors about the use of the antibiotic in question. Only a single antibiotic was the subject of each

visit. At the conclusion of the interview the visited doctor was given a copy of the relevant brochure.

The physician-counselors were recruited by members of the advisory committee and were senior members of the medical community in part time practice. Both the physician-counselors and the drug educator together underwent training in interviewing techniques as well as technical training in the various antibiotics in question. The visits by the physician-counselors were entirely similar to those by the drug educator.

Doctors to be visited were chosen on the basis of their recorded prior Medicaid prescribing histories. Only doctors who had used the antibiotics in question during the previous year were targeted for educational interventions. These doctors were sorted into four groups: those to receive a mailed brochure, those to receive visits by the drug educator, those to receive visits from the physician visitors, and members of a control group who received no educational intervention. The success of the educational intervention was determined by comparing the prescribing practices of the physicians who received educational information with physicians in the control group who had received no information.

Two assessments of the educational program were made. First, the receptivity of the doctors being visited in their offices was recorded on questionnaires by the visitors and by a follow-up telephone call. Second, and more important, the prescribing practices of the doctors was monitored through Medicaid records for the year following the educational interventions. The prescribing of the drugs in question during the year after the educational program was compared with the physicians' use of the same drugs during the year before the educational program.

Results of the Physician Educational Program. Both the drug educator and the physician counselors were well received by the visited doctors in their offices. Over 85% of the scheduled visits could be completed and of these 94% were assessed as "friendly". When contacted by telephone after the educational visit 85% of the doctors described the educational visit as useful. There were numerous comments that doctors were pleased that their professional societies were performing this service, that the information that they received was sure to be accurate and unbiased; doctors even made suggestions as to topics for future visits.

The mailed brochure had no measureable impact on prescribing behavior of the doctors who received it. This, despite the care taken to make the brochure useful and attractive and despite its visible sponsorship by the Tennessee Medical Association and other societies. It was concluded that this type of educational intervention was not successful.

The drug educator was only modestly successful. Although resembling a pharmaceutical sales representative, the drug educator made only one brief visit to each doctor on each antibiotic topic. Although this had a modest beneficial effect in improving prescribing practices, it was less than had been hoped for. It should be noted that pharmaceutical sales representatives depend upon establishing a continuing personal relationship with doctors in order to successfully promote their company's products. This study could not determine whether multiple visits by a drug educator could redirect prescribing practices. However, in a concurrent study, Drs. Avorn and Soumerai (Reference 6) have

demonstrated that educational visits by specially trained pharmacists can have a beneficial effect on prescribing practices. In their study multiple visits were made; one of the drugs whose prescribing was influenced was a member of the oral cephalosporin group.

In contrast to the above, the brief visits by the physician counselors were remarkably successful in reducing the prescribing of both the contraindicated antibiotics and the oral cephalosporins during only a single visit. For the contraindicated antibiotics, the reduction in prescribing which could be attributable to the physician counselor visits was 34% in the average number of precriptions written per doctor. Also, the proportion of doctors prescribing these medications at all was reduced by 18% and the average number of prescriptions written per doctor through the year was reduced by approximately half. When considering the oral cephalosporins, the physician counselors again produced a strong, attributable reduction in the number of patients receiving these drugs per doctor (a reduction of 21%) and in the average number of prescriptions written per doctor during the year (a reduction of 21%). These prescribing reductions lasted throughout the initial year of evaluation. Importantly this beneficial effect of the physician counselors persisted through the second year after the educational intervention. This was a striking result, considering the brevity of the educational visit (less than 15 minutes).

We conclude that doctors in practice are eager for information which is presented in an unbiased and helpful fashion which will aid them in the appropriate use of antibiotics. In our study, the "messenger" was more important than the message. Doctors, when visited by the physician

counselors responded equally well to the message of improved patient care as well as reducing excessive costs. And when they "get the message", and change their behavior, the effect lasts a long time. Indeed, I am unaware of any other brief, educational encounter, on any subject that has been shown to be as effective in changing anyone's behavior as was this 15 minute visit of a doctor in practice by physician counselors representing their professional organizations.

This study demonstrates that a non-punative, educational program sponsored by the medical profession can change patterns of office practice that are inappropriate or excessively costly. It is clear that medical practice can be changed by a variety of means: regulation, reimbursement, and sanctions. Although undoubtedly effective, these methods have obvious disadvantages. The success of the educational interventions conducted in Tennessee and by Drs. Avorn and Soumerai are a challenge to the medical profession and to all parties interested in delivering effective and appropriate medical care. The potential for improving prescribing practices of antibiotics and numerous other drugs by the use of similar educational programs is an exciting one.

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Mr. GORE. Thank you very much. We'll hold off on questions.

Our second witness is Dr. Edward Kass, director of the Channing Laboratory at Harvard Medical School in Boston. Dr. Kass, thank you for joining us today, and please proceed.

[The biographical sketch of Dr. Kass follows:]

BIOGRAPHICAL SKETCH

Dr. Edward H. Kass was born in New York City, December 20, 1917. He received the A.B. and M.S. degrees (bacteriology) in 1939 and 1941, respectively, and the Ph.D. in medical microbiology at the University of Wisconsin in 1943. He was a fellow in physical chemistry at the latter university and employed in a project for the War Manpower Commission and then completed work for the M.D. degree in 1947 at the University of California in San Francisco. He was a member of Phi Beta Kappa and Alpha Omega Alpha, received the Borden Award for undergraduate research and the Gold-Headed Cane for "qualities best exemplifying the physician". After internship at the Boston City Hospital in the Mallory Institute of Pathology and on the Second (Harvard) Medical Service he became a research fellow at the Thorndike Memorial Laboratory and the Harvard medical services of that hospital and was appointed Senior Fellow in Virus Diseases of the National Research Council. Progressively, he became Associate, Assistant Professor, Associate Professor and Professor at the Harvard Medical School and is now the William Ellery Channing Professor of Medicine and Director of the Channing Laboratory. He is the recipient of two honorary degrees, and numerous national and international honors, including membership in the Royal College of Physicians, the Rosenthal Award of the American College of Physicians, a special citation from NASA, and one from the American Heart Association. He has served as Secretary and then President of the Infectious Diseases Society of America, is President of the International Congress for Infectious Diseases, has been Vice-President of the Inter-Science Conference on Antimicrobial Agents and Chemotherapy, Vice-President of the International Congress of Nephrology, Treasurer of the International Epidemiological Association, and has held office in numerous other scientific organizations. He is editor of REVIEWS OF INFECTIOUS DISEASES, was editor of the JOURNAL OF INFECTIOUS DISEASES for 11 years and served on the editorial board of numerous journals including the JOURNAL OF CLINICAL INVESTIGATION, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, PREVENT, INFECTION, and others. He is the author of approximately 400 scientific publications and of eight books, most of them dealing with aspects of infectious diseases and clinical epidemiology.

Dr. KASS. Thank you, Mr. Chairman.

Since you have heard a great deal already on the subject, I'm going to limit myself to a few remarks and leave my testimony as it is, which contains much of my general feeling. I would summarize what I've heard and what I think in a few rather simple statements.

The first is obvious, that resistance is a major problem. The second is equally obvious, that antibiotics are a major boon. Now in practical terms, the tug-of-war that each clinician has to cope with between trying to maximize good and minimize harm gets down to a statement that I believe strongly, which is that no amount of titration between these will give us an exact balance between optimal use and overuse, and no amount of education is going to bring forth guidelines that are so precise that we will exactly hit the target that we're after, which is to have optimal use without overuse.

So we're fundamentally, in practical terms, faced with the problem of on which side are we going to make our errors, and it's quite perfectly obvious to all of us, clinician and nonclinician alike, that if we're going to error, it's going to be on the side of overuse. We're not going to allow lives to be lost simply because we failed to use a drug that might have been useful.

So in that framework, I think we will always have with us the problem of resistance. The practical consequences of this will be to try to determine whether there are ways in which we can deal with this inevitable problem that will minimize some of its effects, that will lower some of its effects, and that will give us maximum return. And that's really what we get down to over and over again as we look at the problem.

And I would offer only a few examples, because only a few exist, to my knowledge, that will help us through this dilemma. One is the type of study that Dr. Schaffner has just given us an insight into, and I think it speaks for itself in its effectiveness and value. The other is the kind of study that my colleagues and I carried on some 10 or so years ago in random hospitals in Pennsylvania. We chose 20 out of the 192 by a pure random method, and looked at how antibiotics were actually used in these hospitals. And this was a representation of all the hospitals. It happened to be two university hospitals in there. And for the benefit of all of us, I think it's worth saying that, at that time, the 2 university hospitals differed not at all in any important respect from the 18 nonuniversity hospitals, small, middle, and large, in how antibiotics were used.

I suspect that this statement may need modification in view of the great acceleration in the amount of immuno-compromised patients that are now showing up in university hospitals. I think this would be one of the important things to be looking at over the next few years. But at least we have a baseline for comparing what's happening now with what happened 10 years ago. It's the type of study that Dr. Hughes and his colleagues are now conducting at the CDC.

But there was one consequence of that study that tells us how we might use techniques similar to the ones that Dr. Schaffner alluded to in his work. We found, for example, that about 30 percent of all antibiotic that's used in hospitals is used for surgical prophylaxis.

That is, it's given to a patient just before or during the procedure to prevent certain types of postoperative infections. And in some clearly specified situations, such prophylaxis has been shown to be effective. In many other situations, we don't really know how effective they are and they're used variably, therefore, by different surgeons.

However, when we looked at how prophylaxis was actually used, we found that the prophylactic drug tended to be ordered and then administered for the remainder of the patient's hospital stay. Now the data are overwhelming in showing prophylaxis is only valuable for that first day surrounding surgery. By simply saying, look, if you limit all orders to a maximum of 24 or 48 hours for prophylaxis and by just cutting off the excess and then rewriting the order if there's a reason to continue the drug, one will save on the order of 25 percent of all drug that's used in hospitals. This amounts to a—a price tag that's measured in the billions, between $1 and $2 billion a year. And to whatever the consequences might be from use where there's no value of a drug in terms of drug toxicity, in terms of adding to the burden of resistance, those benefits will accrue.

So these are ways of using Dr. Schaffner's data and our data. These are illustrations of ways in which one can use the existing system to try to isolate those areas where there is excess use and where there is some adverse consequence from excess use. And one can delineate exactly where the values are.

The bottom line, however, is that I doubt that any of these is going to make a large difference in terms of the total load of resistance or in terms of these large overview effects if you see them. I think they may often account for some of these micro differences that we've seen from institution—institutions or in certain restricted communities in which a very small number of people account for certain types of practice.

I would caution everyone who looks at this problem about this problem of trying to develop guidelines that will be helpful. I happened to cochair a committee with Dr. George Jackson of the University of Illinois that produced a study on behalf of the American College of Physicians that I just referred to, a study of antibiotic uses in random hospitals in Pennsylvania.

Part of the mission of that committee we never did publish, and that was that one group of members of the committee—all, I think, acknowledged experts in infectious diseases—undertook under the guidance of Dr. Jackson, who was an outstanding person in the field, to try to develop guidelines for more effective use of antibiotics that would minimize some of the problems. Well, there were a few guidelines that everyone would agree on. Dr. Schaffner listed some of these, and we later learned more. But in most antibiotic use, the guidelines were so permissive, used so often words like usually or often or sometimes, and so on, that, in fact, they were not very useful at all. And I contend this is the present day state of the art in clinical medicine. And while, of course, education is very valuable and necessary for pinpointing certain problems, the major share of the problem is still with us.

Now what are we going to do about it? First, I would suggest that the real effort has to go into developing methods for quicker and more accurate diagnosis. We still have to wait too long because

of the nature of things to find out whether an infection is due to an organism that is susceptible or resistant. We do our best guess, and we're sometimes wrong. And research aimed at developing much quicker diagnostic methods that will be available within minutes or hours clearly will be valuable, and we're not doing nearly enough of this.

Second, I would suggest that we look very hard—as we're doing, but maybe not enough—on these various mechanisms of resistance that you've heard about. We know that there are certain drugs that cure plasmids. The trouble is that they're so toxic nobody can use them. Other alternatives that will be less toxic, we know that there are ways of inhibiting transfer of plasmids. They haven't been put into practical terms. Are there methods we can develop for inhibiting transfer? We're still left with the problem of transposons that you brought up quite correctly, Mr. Chairman, and Dr. Levy spoke about. Well, yes, they're here, and the reality is there. Are there methods that we can develop for inhibiting, again, their effective penetration into the chromosomal armamentarium of bacteria?

I believe in the long run these are going to be more effective means of approach and this type of research will be more effective than anything else we can hope to do. I believe we can find certain areas by careful looking in which excess use can be minimized.

And then I'd like to raise one other point, since it is in the purview of this committee and represents much of what was discussed yesterday. I hope that we will not waste time on useless adventures that give to some a promise of help and that look from the data as though they'll give no promise.

For example—I use as my example the whole problem of subtherapeutic amounts of antibiotics in animal feed. I happen to be a member of the committee of the National Research Council that you've heard about that examined this problem with, I hope, considerable thoroughness. We came to the conclusion that the therapeutic use of antibiotics was so great that there was no way to find out whether the subtherapeutic amounts of antibiotic had any effect. And given the present general consensus that such therapeutic use of antibiotics is economically useful, we are hesitant to tinker with what looks to be shown to be useful in the name of an effect that, to us, seemed unlikely to show any benefit in terms of human ecology.

The increase in therapeutic use of, for example, tetracycline, that has been recorded in Great Britain where tetracycline has been forbidden from animal feed for the past 12 years, is quite striking. And it's quite clear that the present-day farm practices are such that there are easy mechanisms for spread of pathogens throughout a herd or throughout a flock, and we've all seen this, any of us who've looked at present-day feed lot methods and methods of raising poultry. And while these methods are economically useful to the consumer, they certainly pose substantial hazards to the animals involved. And it's easily understandable in today's farm life that a farmer is going to take no chances with the first dead calf or the first dead chickens. The veterinarian's going to be called and the animals are going to be dosed. And the consequence of this is that we see no substantial decline in the number of resistant bacte-

ria to tetracycline in Great Britain 12 years after tetracycline was removed from animal food. And the reason is quite clearly that the therapeutic use has been so great and so frequent that it retains the tetracycline-resistant organisms in those flocks and in those herds more or less unchanged, and I believe this is the case.

We are at the present looking at this problem from another viewpoint, the possible effect of such resistant bacteria on laboring personnel who have close contact. And we're looking at women who work in a poultry abbatoir, packing house, where in our very incomplete studies the E. coli are about 50—a little over 50 percent resistant to tetracycline, and where, in these women as in all women, there's a fairly high rate of unsuspected urinary infection, which is something I've been studying for a good many years.

And when we isolate in a group of the first 40 women the bacteria that are causing their urinary infection, we had only 2 of the 40 that were resistant in the same way that over half the organisms were in the chickens, and one of the two was a woman who had a long history of multiple use of antibiotics, an ample basis for understanding the resistance. The one that's left is the one we're still studying, and we'll know more about whether her plasmids are similar to the plasmids in the chicken, and we'll know this relatively soon. But it certainly indicates that there is not a high risk of acquiring resistant bacteria in human infection, despite this intense and prolonged day-to-day contact.

Incidentally, all of the subjects in this study were people who had worked in this plant for a minimum of 3 months.

So, I think my final statements here, that we are going to be forced to live with this problem, that our strategies for coping with it will have to be varied and we'll have to depend on new information, that our biggest problem is ignorance and inadequate research for finding real solutions, and that quick and dirty fixes based on inadequate data are almost certainly going to clutter up the situation that give us very little real relief from the problem as it exists.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Kass follows:]

TESTIMONY BEFORE THE
COMMITTEE ON SCIENCE AND TECHNOLOGY

U.S. HOUSE OF REPRESENTATIVES

ALBERT GORE, JR.
CHAIRMAN
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

BY
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How scientific evidence is used in the setting of public policy continues to be a concern to the public, to policy making officials and to scientists alike. In the following statements I shall focus on two general areas in relation to the effect of antibiotics and the resistance to antibiotics on human health.

The first deals with the problem of use and abuse of antibiotics in hospitals. There can be no doubt that resistance of bacteria to many antibiotics is a regular occurrence in hospitals. A large part of the research in academic and industrial laboratories has been directed on the one hand to methods for keeping to a minimum the emergence of resistance and on the other to development of new drugs that will counteract the effects of resistance either by inhibiting a mechanism whereby bacteria become resistant or by developing new drugs that will attack bacteria that are resistant to existing drugs. That we have been able to keep ahead of bacterial resistance, on the whole, is a tribute to the skill and ingenuity of the pharmaceutical houses in which virtually all new drugs have been developed. However, the development of each new drug entails increasing expense and there is always the fear that this process, rapid in the past, may slow down simply because we may have reached something closer to the end of what we can achieve by development of new drugs. So there is understandable concern about minimizing resistance by attempting to reduce needless use of antimicrobial drugs. Many papers have been written about use and abuse of antimicrobial drugs and everyone agrees that abuse is harmful. The trouble is that it is a little like agreeing that sin is bad: it is not always so easy to define sin.

Antibiotics are among the greatest lifesaving drugs that are known and have completely revolutionized the care of the sick. Approximately one third of all patients in American hospitals receive antibiotics for one reason or another, and close to half of all antibiotic use in this country takes place in hospitals, for understandable reasons. When a patient is acutely ill, and it is not entirely clear what the nature of the disease is, the tendency is to use antimicrobial drugs whenever there is the slightest suspicion of infection. It is difficult to quarrel with this tendency since antibiotics are in general relatively low in toxicity and high in effectiveness. After the infecting microorganism has been isolated and identified, we sometimes discover that we have made the wrong guess. If there is time, the antibiotic may be switched to one that is more likely to be effective. No single antibiotic and no known combination of antibiotics will protect against every known infection and since the symptoms and signs of infection are not always specific for one or another kind of bacterium, we essentially are forced to use our best judgement and best guess—inevitably some errors in judgement will occur and part of the research that is going on and that has been conducted over the past 40 years has been directed toward more accurate and more rapid methods of diagnosis so that we can keep the mistakes down to a minimum.

The high value of antibiotics means that a large number of patients in hospitals will receive these drugs and no amount of cautionary teaching will diminish this use. My coworkers and I have felt that the sensible approach to the problem of resistance, from this viewpoint, is to try to identify those areas in which excess use can be documented in ways in which there is virtually no controversy. An example of this has been in our

studies of the use of prophylactic antibiotics.

Prophylactic antibiotics are given to a large share of patients undergoing surgical procedures. About 30% of all antibiotic use in hospitals goes for prophylaxis. There is strong scientific evidence that prophylaxis is valuable only when it is given just before and during an operative procedure and therefore is valuable only during the first day when surgery has been performed. Continuing prophylaxis after the first day has, in repeated clinical and experimental observations, had no benefit but, of course, the longer the patient receives the drug whether beneficial or not the greater is the chance that the patient will develop some type of hypersensitivity to the drug and the greater is the chance that resistant bacteria will be selected. Our research showed that in most hospitals, when a prophylactic drug had been ordered it tended to be continued for as long as the patient was in the hospital. This meant that about 90% of all prophylactic drug was being used at a time when it had no conceivable benefit but might conceivably do some harm. By simply documenting this and calling it to the attention of our colleagues in our hospital and in a neighboring hospital, we found that the excess use of prophylactic antibiotic in relation to surgery was reduced to about 8%. How widespread this reduction in use has been is difficult for us to document because this type of research has received relatively little funding even though it has substantial economic and medical implications. The research does point the way, however, to how substantial savings, which we estimated at well over one billion dollars a year, might be achieved with reduction in risk to patients.

Similar places in which excess use of antibiotics or use that seems to be harmful, can be documented. However, it must be stated clearly that these various areas that we have called excess still account for only a minority of antibiotic use and that the great majority of such use will continue for reasonable medical reasons. Therefore resistance to antibiotics will be a continuing problem for the foreseeable future in hospitals. Our task is simply to try to keep resistance to a minimum by judicious reduction of excess. I do not see that this is an area for legislative action, in that it involves education, further research, and the transmission of the results of these to the medical profession. It would be almost impossible to conceive of legislation that would address this type of problem.

A second problem that has received a great deal of recent attention deals with whether much of the resistance of bacteria to antibiotics in our country could be due to the use of subtherapeutic amounts of antibiotic in animals feeds.

In order to put the problem into its framework, I wish to submit the following statements. Many of them are taken directly from the report of a Committee of the National Research Council of the National Academy of Sciences, on which I served. The Committee spent a long time reviewing the complex literature, brought in experts from the scientific community, and interviewed farmers and public servants, and came to a conclusion that may be frustrating but is nevertheless, in my opinion, the only reasonable statement that can be made at this time.

The difficulty encountered by the Committee can be summarized in a few

statements. The first is that present day practices in raising livestock have been increasingly efficient and have accounted for the relatively low cost of animal protein in the American diet. These methods however, involve shipment over long distances for certain types of livestock and involve raising the animals in such close quarters that any infection may sweep through a herd or flock with catastrophic results to the farmer. I do not pretend to be an expert on farm practices and have assumed that the present methods are the most efficient and cost effective methods available to American farmers.

Numerous studies have demonstrated that subtherapeutic amounts of antibiotic in animal feed improve the rate of growth of young farm animals, decrease mortality, and decrease diseases such as "hoof rot" and liver abscess that are common in various farm animals brought to slaughter.
Economic estimates have indicated that if these beneficial effects of subtherapeutic amounts of antibiotics in animal feed were removed, the cost of animal protein would rise by approximately 15%. Since the cost of animal protein has a profound effect on the amount sold, it is estimated that losses due to the elimination of these low levels of antibiotics in animal feed would amount to something between 1.5 and 4 billion dollars annually.

It is in this framework of demonstrated value that the problems associated with the use of such antimicrobial drugs must be examined.

The principal problem consists of the possible role of antibiotics in fostering the appearance of resistant bacteria in livestock. Since livestock contain bacteria such as Salmonella that are pathogenic to humans, the problem of potential risk to the consumer must be examined carefully. Secondly there is the concern that there may be some residual antibiotics in the animal protein that is consumed. Thirdly there have been concerns that the type of animal protein developed under conditions of antibiotic use might be nutritionally inferior because the animals grow faster. The last of these we can discard because no evidence has ever been developed to support such a claim. In fact since antibiotics admittedly lead to healthier and faster growing animals one would expect that the protein would be fully nutritional.

The problem of residual antibiotics in the meat has been dealt with by quite stringent regulations and many field studies have shown that the amount of antibiotic in meat is generally at low levels such that ordinary cooking destroys what small residual there may be. Of course, there may be farmers who transgress the law. This is a separate problem that requires education and enforcement.

The most important consideration that has been raised has to do with the role of antimicrobial drugs in animal feed in fostering antibiotic resistance among the bacteria harbored by the livestock. It is this question that should occupy us most because of its implications in terms of human health. Unfortunately the analyses indicate that it is impossible to determine how much effect subtherapeutic amounts of antibiotic have on antibiotic resistance. The overwhelming reason why it is impossible to assess this effect is because there are no restrictions, and probably there should be none, on the use of antibiotics to treat sick farm animals. The data indicate that even in countries such as Great Britain, in which drugs such

as tetracycline may not be added to animal feed and have not been added to animal feed for the past 12 years, the rate of tetracycline resistance in the bacteria of farm animals has remained at higher than 95% of the micro-organisms harbored by these animals. The reason clearly is that since the therapeutic use of tetracycline has not been restricted, farmers who are apprehensive about the health of their animals, seeing the first evidence of illness, have called upon veterinarians to treat the entire herd or flock and the use of tetracycline for veterinary purposes in Great Britain has risen steadily through the past years. No one who has examined the problem of antibiotic resistance will deny that the therapeutic use of antibiotics, in hospitals and in agricultural settings, selects toward resistance of the bacteria of the livestock. While there may be some validity to the statement that antibiotics may sometimes be misused or overused, no one can reasonably doubt that antibiotics are among the major lifesaving medical tools whether in human or veterinary medicine and that even under the most carefully delineated circumstance, a large amount of antimicrobial drugs will continue to be used for therapeutic purposes. It is this therapeutic use, at levels many times higher than those found in the subtherapeutic levels of animal feed, that has made it impossible to determine whether the smaller increment that might conceivably come from the subtherapeutic amount of antibiotic in animal feed has any significance at all.

One cannot doubt that livestock often harbor Salmonella and that a certain percentage of these Salmonella may be antibiotic resistant. One cannot doubt that an individual infected with such resistant Salmonella may occasionally become ill. Fortunately for us, our methods of refrigeration and of cooking makes such an illness relatively uncommon, despite the huge amounts of animal protein that we consume. In most instances, the appearance of salmonellosis usually occurs under circumstances in which the Salmonella have been permitted to multiply in the food to very high levels, when the food has been improperly refrigerated, improperly cooked or in other ways improperly handled so that the Salmonella may multiply to levels that are likely to cause infection. What is unclear at the present time is whether this resistance among Salmonella is significantly affected by the subtherapeutic amount of antibiotic in animal feed. It is my judgement that this effect must be exceedingly small compared with the much larger effect of the widespread therapeutic use of antibiotics in livestock.

Recently a publication has appeared from the Centers for Disease Control and from the Minnesota Health Department suggesting that an outbreak of salmonellosis was due to the subtherapeutic amount of antibiotic in the animal feed. I have discussed this paper with one of the co-authors. He has agreed that the data as presented offer no way to distinguish between the therapeutic and subtherapeutic amounts of animal feed that these animals might have received. There is no way to determine from the history of these animals what might have occurred in the past. It should be pointed out that even if farm animals are brought to a farm where the animal feed does not contain antibiotics, it may take months or years before the resistant bacteria with which they arrived are eliminated from that herd or flock. Since resistance is virtually universal, and the young animals acquire this promptly from their immediate environment, simply putting the animals into an environment free of antibiotics does not relieve the problem.

It is also true that when farm animals are raised under optimal conditions of sanitation and feeding, the beneficial effect of subtherapeutic amounts of antibiotic is small and often not demonstrable. However, the farmers have made clear that such optimal conditions are themselves so expensive and difficult to maintain that they are economically not feasible and that the use of subtherapeutic amounts of antibiotic are much more realistic for them at the present state of our development.

I would suggest that the conclusions drawn from the recent paper in the NEW ENGLAND JOURNAL OF MEDICINE and in the accompanying editorial were not appropriate conclusions for the reasons that I have outlined above. That it would be exceedingly important to know more about why subtherapeutic amounts of antibiotic are useful is clear. Relatively little research on this important subject is going on and more should be encouraged with the hope that one day it would not be necessary to use any such additives in order to reduce the toll of illness in livestock. Nevertheless, at the present state of our information, to deny farmers the use of this admittedly effective method of raising livestock, to cause the price of animal protein to rise with its economic and nutritional consequences, and to face whatever consequences might accrue further from the removal of small amounts of antibiotic from animal feed would represent a judgement that was based on no substantial evidence of harm and substantial evidence of good. Since the overwhelming effect of the therapeutic use of antibiotic is what it is, and since there is no reasonable basis for interfering with such therapeutic antibiotics, we must face the fact that resistant bacteria will be with us until we learn more about the fundamental mechanisms of resistance and find ways to overcome these mechanisms. Removing a tiny fraction of all of the antibiotic use is unlikely to make a significant contribution toward our solution of this important problem in human and veterinary medicine.

Mr. Chairman, I have tried to make two basic points. The first is that the therapeutic use of antibiotics is so obviously beneficial that inhibition of such use should be limited to those areas in which there is clearly proven benefit from such an inhibition. This should not be a matter of opinion or of guesswork but should follow from clear and unequivocal data. I have indicated that under the present circumstances of use of antibiotics a certain amount of resistance in bacteria is inevitable and that continued research will be necessary in order to apply a variety of different strategies toward control of this resistance. The second point I have tried to make is that the subtherapeutic amount of antibiotic in animal feed cannot be evaluated in terms of its contribution to the resistance problem. This is because the therapeutic use of antibiotics in farm animals is so great that it is not possible to determine what effect the relatively smaller amounts of antibiotic in animal feed might have in relation to the problem of resistance. Since subtherapeutic amount of antibiotics really seem to be beneficial, since removing them would raise substantially the price of animal protein, with its many economic consequences, it would seem unwise to prohibit such use until better and more substantial evidence were obtained. We must try to determine whether subtherapeutic amounts of animal feed make any significant contribution to the problem of resistance, under the circumstances that exist in farms, and whether the resistant bacteria that are inevitably accumulating in livestock because of the therapeutic practices pose any substantial risk to human health. In the absence of convincing data in any of these directions it would seem to me that legislative action is neither wise nor warranted. Thank you.

Mr. GORE. Thank you very much.

Our third witness on this panel is Dr. Sidney Wolfe, Director of Public Citizen Health Research Group. We've worked with you on many occasions, Dr. Wolfe. We're delighted to have you here, and please proceed.

Dr. WOLFE. I'd like to add something to what the minority counsel said. He complimented you on your legislative efforts. I would like to talk about something I think is much more important.

In the health and safety area particularly, I don't think the problem in the United States is the lack of good laws. The food safety laws, drug laws, occupational health laws and environmental laws, I think, are quite adequate. The problem is a lack of enforcement, particularly more recently a lack of putting out the kinds of regulations that the laws intended. And I think that the legacy that you are leaving as you end this hearing today in the House is sort of an unparalleled one in the House in terms of oversight, the oversight of the laws that are already on the books. And I think that the difference that you made with all these hearings is bringing attention back to what I think is the more important purpose of the legislature, which is oversight, not passing new laws.

I fervently hope that in your new job, sooner rather than later, you will once again be able to hold such hearings.

Mr. GORE. We will hold the record open so that you can revise and extend those remarks. [Laughter.]

Thank you. Thanks for your kind words.

Dr. WOLFE. It's unfortunate enough that tons of antibiotics used without a prescription are dumped each year into healthy animals, increasing the likelihood of antibiotic-resistant bacteria which can injure or kill people who later become infected by these micro-organisms. And we strongly support the petition to ban these subtherapeutic uses of animal—antibiotics in animals.

I think, despite what Dr. Kass said, the concept of "subtherapeutic use of antibiotics" is not that much different in animals than in humans in the sense that—and I'll go into that in minute—when you take a large number of people who have colds and you give them antibiotics, it is dumping into them something for which there is no arguable benefit—just a common cold, not a complication of—thereof. Similarly, in terms of treating infections or whatever in cattle, there isn't really any arguable benefit. The fact that in Great Britain there hasn't been a decrease in tetracycline resistance during the interval where the subtherapeutic use has been banned, I don't think is a complete story because it is not unlikely that one might have seen continued increase instead of the, I guess, leveling off that occurred had they not done that.

But even more tragic and dangerous, and certainly the subject of today's hearing, is the dumping and misuse of tons of human antibiotics on people as "treatment" for diseases which do not call for any antibiotic—any antibiotic or, in other instances, for diseases which would be more properly treated by a different antibiotic, or, as mentioned earlier, using an antibiotic for much longer than one needs in the case of those circumscribed instances where prophylaxis is appropriate.

This dangerous dumping of antibiotics into people is quarterbacked not by farmers, but by doctors in white coats with the sig-

nals often being called by drug companies on the sidelines. Again, I'll give a specific example in the case of an antibiotic, clindamycin, lincomycin, where there was a promotion of what turned out to be a misuse and should have been known to be such at the time, a promotion by the drug company making it.

Aside from wasting hundreds of millions of scarce health dollars a year, misprescribing of antibiotics has three types of adverse health consequences: One, preventable adverse drug reactions in people who should not have had any antibiotic or should have had a less dangerous but equally effective antibiotic instead of the one they were given; two, increased mortality or illness in people whose infection is inadequately treated because the wrong antibiotic is used; and three, increased prevalence of antibiotic-resistant bacteria—because of overuse and or misuse of antibiotics—which can injure or kill people who are infected with these harder-to-treat bacteria.

The first thing to note, which is simply a description of what's happened, is that there has been a 100-percent increase, or doubling, in the prescriptions of antibiotics during the interval 1964 to 1983 in the United States. This is obviously completely out of proportion to either the increase in population or even the increase in the older part of the population.

And second, there's been an elevenfold increase in fatal blood infections, or septicemia, during the interval 1950 through 1983, or to compare it to the interval that I just mentioned in terms of the doubling of the use of antibiotics, a 3.4-fold increase in the age-adjusted rate of septicemia from 1964 through 1983.

If you look at the National Center for Health Statistics' data on age-adjusted causes of death over the last 30 years or so, one sees that, by far and away, septicemia is the most rapidly increasing cause of death in the United States, exceeding in its rate of increase even cancer—which has gone up slightly—homicides and chronic obstructive lung disease. According to data from HHS's National Center for Health Statistics, as I mentioned, there's been an elevenfold increase in the age-adjusted death rate from septicemia from .3 per 100,000 people age adjusted in 1950, to 1 in 1964, to 3.4 in the last year for which there is data, in 1983. In 1983, there were 13,350 cases of septicemia recorded on death certificates as the cause of death, according to the National Center for Health Statistics data. And it's generally agreed that these figures greatly underestimate the actual number of cases because of incomplete death certificate recording.

Dr. Hughes went over the NNIS surveillance data. He didn't go over the mortality data. If you use the three categories of hospitals, nonteaching hospitals, and then the large and small teaching hospitals, and within each category project their death data nationally, you get for the interval that they published 1980 through 1982 approximately 37,200 deaths per year. This is all nosocomial infections, not just the ones that are in the blood, septicemia. And, as he mentioned, in certain kinds of bacteria, there was even during the short interval an increase in the frequency of antibiotic resistance, particularly in the large hospitals—large teaching hospitals.

Now relating the simultaneous doubling of antibiotic prescriptions with tripling of deaths from septicemia is not, by any means,

meant to imply that the increased use of antibiotics and the subsequent or concomitant increase in antibiotic-resistant bacteria is the sole cause of the rise in death, the sharp rise of deaths from septicemia.

In addition to something Dr. Kass just mentioned, the increased use of immunosuppressants in patients in hospitals, steroids and immunosuppressant drugs used for treating cancer, there's also increased use of indwelling catheters which can also be an increased source of septicemia. So although these other factors do exist and can account for part of the problem, I think that when all is said and done, it will be shown that the misprescribing, and overprescribing of antibiotics are another factor, and perhaps one about which something can be done.

I'd just like to cite several examples, and I call them gross examples because I think they are gross examples, or examples of gross misprescribing. They coincide to some extent with the local, highly successful experiments that Dr. Schaffner and his colleagues have done.

One, the common cold. In table 1 of our testimony, look at 1983 U.S. data on prescriptions written by doctors for treatment of the common cold, a viral infection for which no antibiotic's been shown to be effective. Of approximately 3.3 million patients who saw doctors for treatment of the common cold, about 51 percent, or 1.7 million, were given a prescription for an antibiotic, wasting well over $15 million, placing these people at risk of adverse reactions to drugs, and increasing the likelihood of antibiotic-resistant bacteria. Some of the more commonly used drugs for the common cold were amoxicillin, erythromycin, ampicillin, cephalosporin is 124,000 prescriptions and most expensive of the group, tetracyclines, and so on.

A second example is lincocin or lincomycin. This antibiotic has been linked to hundreds of cases of pseudomembranous colitis and dozens of deaths. Despite a box warning saying "it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate," 879,000 prescriptions were written in 1983 for conditions such as colds, sore throats, and uncomplicated ear infections and other upperrespiratory infections, noted as URI's on the chart in table 2.

These prescriptions, the inappropriate ones, made up 56.2 percent of all prescriptions written for the drug. Although the manufacturer of the drug, Upjohn, was belatedly forced to include the above warning label, and had—it's been there for some time, prior to that, fully aware that the drug had killed and injured people from pseudomembranous colitis, the company was actively promoting it for treatment of upper respiratory infections and doctors were responding by using it for treating upper respiratory infections. So although that has been eliminated 8 or 9 years ago, I believe, we still see that, in 1983, the bad habits stay there. Many doctors apparently remember the earlier promotion, have not yet been yanked out of their bad prescribing habits by the newer box warning.

A third example, tetracyclines, also mentioned by Dr. Schaffner as something that probably shouldn't be prescribed certainly for children. In 1975, the American Academy of Pediatrics in its jour-

nal Pediatrics, in an article I think entitled "Requiem for Tetracycline," recommended against use of the antibiotic tetracycline by children less than 8 years of age saying, "There are few, if any, reasons for using tetracycline in children less than 8." It can cause, as mentioned by Dr. Schaffner, permanent staining of the teeth and, according to the American Academy of Pediatrics, temporary inhibition of bone growth. Despite this, 8 years later, 1983, there were still 129,000 prescriptions written for children 9 or less. I use the figure 9 or less because that's the age category that this data is broken out in. It's unlikely that most of them are just age 9.

The fourth example, also one mentioned in the Tennessee investigations and reeducation by Dr. Schaffner, is chlorampenicol. As mentioned, this antibiotic has been known for 25 years to cause rare, but fatal, bone marrow toxicity, aplastic anemia, was prescribed 445,000 times in 1983. In some of these instances, it was an important drug, such as for treating Salmonella and in certain kinds of meningitis. But as seen in table 3, 49 percent of the prescriptions, or 220,000 were for indications for which the drug is clearly not indicated, such as tonsillitis and infection prevention after surgery.

These are but a few examples, based on outpatient prescribing, of the misuse of antibiotics by doctors. Even more studies have focused on misprescribing of antibiotics in hospitals where, according to some of the surveys, many antibiotic treated patients raising—ranging in different studies from 30 to 60 percent, especially on surgical wards, had no clear-cut evidence of infection. And this goes far beyond just the prophylaxis in surgical patients in most categories, as mentioned by Dr. Kass, where some antibiotic may be appropriate.

In summary, there is clear evidence of a massive misprescribing of antibiotics. Every feasible approach must be used to prevent this expensive and dangerous epidemic. Three suggestions are as follows:

One, Government-sponsored counterinformation. As accomplished by Dr. William Schaffner, his colleagues, and Dr. Avorn and his colleagues at Harvard, there should be a significant expansion of cost-effective efforts to reverse the drug company induced misprescribing by many physicians by means of attractive counter ads, and especially by personal visits from doctors or pharmacists.

I would add that just as the pro—the problem of antibiotic resistance is an international one which needs international attention, the solutions, obviously, are the same. And at a recent NIH conference sponsored by the Fogerty Center, there were a number of exciting examples in other countries such as Australia and elsewhere of efforts to change doctors' prescribing habits which were both cost effective and successful.

Two, the FDA should order drug companies to include mandatory patient package inserts on all antibiotics so that proper indications for use and information about risks are known to patients. It is difficult to think of a class of drugs for which this is more needed, given the fact that so many of the prescriptions are written for diseases for which the drug is clearly not indicated, and certainly the patient is the most interested party in trying to reverse this.

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If they knew from a simply worded patient package insert, I think they would do something about it.

Third, much better education of physicians and, of course, all other health professionals, in medical school and afterward about proper prescribing of antibiotics is needed.

Thank you very much.

[The prepared statement of Dr. Wolfe follows:]

PublicCitizen

Congress Watch • Critical Mass Energy Project • Health Research Group • Litigation Group • Tax Reform Group

STATEMENT OF SIDNEY M. WOLFE, M.D.
DIRECTOR, PUBLIC CITIZEN HEALTH RESEARCH GROUP
BEFORE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT
HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY

HEARING ON
ANTIBIOTIC MISUSE AND ANTIBIOTIC RESISTANCE

DECEMBER 19, 1984

Chairman Gore and Members of the Subcommittee,

Thank you for the invitation to present my views on the serious epidemic of misprescribing of antibiotics which, along with the misuse of these drugs in animals, are the most important preventable causes of antibiotic-resistant infections. It is unfortunate enough that tons of antibiotics, used without a prescription, are dumped each year into healthy animals, increasing the likelihood of antibiotic resistant bacteria which can injure or kill people who later become infected by these microorganisms. We strongly support the petition to ban these sub-therapeutic uses of antibiotics in animals.

Even more tragic and dangerous, however, is the dumping and misusing of tons of human antibiotics on people as "treatment" for diseases which do not call for any antibiotic or, in other instances, for diseases which would be more properly treated by a different antibiotic. This dangerous dumping of antibiotics into people is quarterbacked not by farmers but by doctors in white coats with the signals often being called by drug companies on the sidelines. Aside from wasting hundreds of millions of dollars a year of scarce health dollars, misprescribing of antibiotics has three types of adverse health consequences:

1. Preventable adverse drug reactions in people who should not have had any antibiotic or should have had a less dangerous but equally effective antibiotic instead of the one they were given.

2. Increased mortality or illness in people whose infection is inadequately treated because the wrong antibiotic is used.

3. Increased prevalence of antibiotic resistant bacteria (because of overused, misused antibiotics), which can injure or kill people who are infected with these harder-to-treat bacteria.

100% Increase in Prescribed Antibiotics: 1964-1983

During the past 20 years, there has been a 100% increase (a doubling) in the number of prescriptions filled for antibiotics in the United States. According to the drug industry's own internal marketing data, (Lea, Inc. Ambler Pa for 1964 and IMS Inc., Ambler, PA for 1983) the number of antibiotic prescriptions rose from 100 million in 1964 to 201 million in 1983.

11-Fold Increase in Fatal Blood Infections (Septicemia): 1950-1983 (3.4 Fold Increase, 1964-1983)

Septicemia (blood infection) is by far the most rapidly increasing cause of death in the United States, exceeding, in its rate of increase, cancer, homicides, and chronic obstructive lung disease. According to data from HHS's National Center for Health Statistics (Final Data NCHS Vol. 33 #3, Supplement, June 22, 1984 & Vol. 32 #13, Sept. 21, 1984) there has been an 11-fold increase in the age-adjusted death rate from septicemia, increasing from 0.3 cases per 100,000 age-adjusted population in 1950 (1.0 case per 100,000 in 1964) to 3.4 cases per 100,000 in 1983. In 1983 there were 13,350 cases of septicemia recorded on death certificates as a cause of death according to N.C.H.S. data. It is generally agreed that these figures greatly underestimate the actual number of cases because of incomplete death certificate recording.

These are only those deaths from blood infections. According to national projections from a study on all types of nosocomial infections (hospital acquired) by HHS's Centers for Disease Control (C.D.C. Surveilance Summary Vol. 32 #4SS) the total number of fatalities per year in hospitals from hospital-acquired infections, in which the infection either caused or contributed to the patient's death, was 37,200 deaths per year. Although these data are only for 1980 - 1982, even during this short interval there was an increase in the frequency of certain types of antibiotic resistant bacteria.

Relating the simultaneous doubling of antibiotic prescriptions with tripling of deaths from septicemia is not meant to imply that increased use of antibiotics, and the subsequent increase in antibiotic-resistant bacteria are the sole cause of the sharp rise in deaths from septicemia. Although there are other factors, I believe an important one which we can do something about is antibiotic misprescribing.

EXAMPLES OF GROSS MISPRESCRIBING FOR ANTIBIOTICS

1. COMMON COLD: In Table 1, 1983 U.S. data are presented for prescriptions by doctors written for treatment of the common cold, a viral infection for which no antibiotic has been shown to be effective. Of 3,327,000 patients who saw doctors for treatment of the common cold. 1,698,000 or 51% of these people were given a prescription for an antibiotic, wasting well over 15 million dollars, placing these people at risk of adverse reac-

tions to the drugs and increasing the likelihood of antibiotic resistant bacteria.

TABLE 1

MISPRESCRIBING OF ANTIBIOTICS
FOR THE COMMON COLD*

Antibiotic	Prescriptions Sold
Amoxicillin	575,000
Erythromycin	439,000
Ampicillin	184,000
Cephalosporin	124,000
Penicillin G	113,000
Penicillins V & VK	81,000
Tetracyclines	79,000
Tetracycline congeners	103,000
	1,698,000

Total number of antibiotic prescriptions for the common cold: 1,698,000
Estimated number of patient visits for the common cold: 3,327,000
Percent of patient visits for the common cold resulting in the prescribing of an antibiotic: 51.0%

*National Disease and Therapeutic Index, I.M.S., Ambler, Pennsylvania, 1983.

2.Lincocin: This antibiotic has been linked to hundreds of cases of pseudomembranous colitis and dozens of deaths. Despite a box warning saying "it should be reserved for serious infections where less toxic antimicrobial agents are innapropriate", 879,000 prescriptions were written in 1983 (as seen in Table 2) for conditions such as colds, sore throats, uncomplicated ear infections and other respiratory infections. These prescriptions made up 56.2% of all prescriptions written for the drug. Although Lincocin's manufacturer, Upjohn, was belatedly forced to include the above warning label, prior to that, fully aware that the drug had killed and injured people, they were actively promoting it for treatment of upper respiratory infections. Many doctors apparently remember the earlier promotion and have not yet been yanked out of their bad prescribing by the newer box warning.

TABLE 2

MISPRESCRIBING OF LINCOCIN -- 1983*

INFECTIONS

Indication	Prescriptions Sold
Acute URI, multiple sites	329,000
Other acute pharyngitis	174,000
Acute tonsillitis	80,000
Common Cold	40,000
Sore throat, unqualified	26,000
Other diseases, upper respiratory tract	16,000
Chronic nasopharyngitis	4,000
Influenza, no respiratory symptoms	3,000
Otitis media, no other symptoms	79,000
Acute otitis media, no mastitis	8,000
Conjunctivitis	5,000
Otitis externa	4,000
Other inflammatory disease of ear	4,000
Meniere's Disease	3,000
Strep sore throat	36,000
Other viral disease	10,000
Tick borne typhus	5,000

NON-INFECTIVE DISORDERS

Indication	Prescriptions Sold
Hay fever from pollen	12,000
Asthma unqualified	7,000
Allergic pharyngitis	4,000
Allergic bronchitis	4,000
Varicose veins, lower extremity	6,000
Surgical aftercare (infection prevention)	11,000
Symptoms and senility	8,000
Neoplasms	1,000

Total number of inappropriate prescriptions: 879,000
Total number of prescriptions sold: 1,565,000
Percent misprescribing: 56.2%

Box Warning in 1984
Physicians' Desk Reference:

WARNING

Lincomycin therapy has been associated with severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the Indications Section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic associated colitis. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition. Vancomycin has been found to be effective in the treatment of antibiotic associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dose is 500 milligrams to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days. Cholestyramine or colestipol resins bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with lincomycin.

*National Disease and Therapeutic Index, I.M.S., Ambler, Pennsylvania, 1983.

TABLE 3

MISPRESCRIBING OF CHLORAMPHENICOL -- 1983*

INFECTIONS

Indication	Prescriptions Sold
Acute tonsillitis	21,000
Other diseases, upper respiratory tract	17,000
Otitis media, no other symptoms	16,000
Acute otitis media, no mastitis	4,000
Chronic otitis media, no mastitis	1,000
Otitis externa	2,000
Glandular fever	21,000
Herpes zoster	3,000
Diseases of the skin and cellular tissue	7,000
Peritonitis	5,000
Acute osteomyelitis	3,000

NON-INFECTIVE DISORDERS

Indication	Prescriptions Sold
Subarachnoid hemorrhage	8,000
Surgical aftercare (prevention of infection)	81,000
Symptoms and senility	24,000
Effects of foreign bodies	4,000
Neoplasms	3,000

Total number of inappropriate prescriptions: 220,000
Total number of prescriptions sold: 445,000
Percent misprescribing: 49.4%

Box Warning in 1984 Physicians' Desk Reference:

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the Indications section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat, or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

*National Disease and Therapeutic Index, I.M.S., Ambler, Pennsylvania, 1983.

3.Tetracyclines: In 1975, the American Academy of Pediatrics (Pediatrics55, 142-3) recommended against the use of the antibiotic tetracycline by children less than eight. "There are few, if any reasons for using tetracycline in children less than eight years old." The reasons against using it are that it can cause permanent staining of the teeth and according to the American Academy of Pediatrics, "temporary inhibition of bone growth". Despite this, eight years later in 1983, there were 129,000 prescriptions written for children nine or less.

4. Chlorampenicol: This antibiotic, known for 25 years to cause fatal bone marrow toxicity, was prescribed 445,000 times in 1983. As seen in Table 3, 49% of these prescriptions (220,000) were for indications for which the drug is clearly not indicated, such as tonsillitis, and to prevent infection after surgery.

These are but a few examples, based on out-patient prescribing, of the misuse of antibiotics by doctors. Even more studies have focused on misprescribing of antibiotics in hospitals "where many antibiotic-treated patients (ranging from 30% to 60%), especially on the surgical wards, had no clear-cut evidence of infection". (J.A.M.A. 1974, 227 p. 1023 - 1032)

SUMMARY

There is clear evidence of massive misprescribing of antibiotics. Every approach which is feasible must be used to prevent this expensive and dangerous epidemic. Three suggestions are as follows:

1. Government-Sponsored Counter-Information

As accomplished by Dr. William Schaffner of Vanderbilt and Dr. Jerry Avorn at Harvard, cost effective efforts to reverse the drug-company induced misprescribing by many physicians with attractive counter-ads and, expecially, by personal visits from doctors or pharmacists.

2. There should be mandatory patient package inserts (PPIs) on all antibiotics so that proper indications and information about risks are known to patients.

3. Much better education of physicians in medical school and afterward about proper prescribing as opposed to misprescribing of antibiotics is needed.

Thank you.

Mr. GORE. Thank you very much.

Our final witness is Joseph Stetler, president of the Pharmaceutical Manufacturers Association; accompanied by Dr. John Jennings, vice president for science and technology with PMA. Always a pleasure, Mr. Stetler, and please proceed.

[The biographical sketches of Mr. Stetler and Dr. Jennings follow:]

C. JOSEPH STETLER
President
Pharmaceutical Manufacturers Association

Mr. Stetler was born in Wapakoneta, Ohio. He received his LL.B. Degree from Catholic University in Washington, D.C. in 1938 and in 1940 received his LL.M. from the same school. He also attended George Washington University and the Benjamin Franklin School of Accounting in Washington, D. C. He received an Honorary Doctor of Science in Pharmacy Degree from the Massachusetts College of Pharmacy in 1979.

Admitted to the Bar of the District of Columbia and the State of Illinois, he is a member of the Chicago, Illinois, District of Columbia, and American Bar Associations.

From 1935-51, Mr. Stetler was employed by various agencies of the Federal government. During the years from 1951 to 1963, he was General Counsel and Director of the Legal and Socio-Economic Division of the American Medical Association.

He joined the staff of the Pharmaceutical Manufacturers Association in 1963 as Executive Vice President and General Counsel. He served as President of the Association from December 1965 until July 1, 1979. He reassumed the Presidency of the Association on October 1, 1984.

On November 1, 1979, he became a partner in the law firm of Munsey, Samuel & Stetler in Washington, D. C. This firm merged in June 1981 with Dickstein, Shapiro & Morin, where Mr. Stetler served as a partner until September 30, 1984.

Mr. Stetler is co-author of the books Doctor, Patient and the Law and the Handbook of Legal Medicine.

Mr. Stetler served as a member of the Reagan-Bush Health Policy Advisory Committee in 1980-81 and was appointed by HHS Secretary Schweiker as a member of the Social Security Advisory Council in 1983. He is also a member of the Board of Directors of Project HOPE, Millwood, Virginia.

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JOHN JENNINGS

M.D., 1949, College of Physicians & Surgeons, Columbia University

Rotating Internship - Jersey City Medical Center

Residency in Internal Medicine - Bronx VA Hospital, 1950-1954, interrupted by service as Army Medical Officer, 1951-1952

Served as VA Staff Physician in East Orange and then entered private practice in 1958

Director of Medical Education at St. Josephs Hospital, Paterson, N.J. and Instructor in Medicine at New Jersey College of Medicine

Joined FDA in 1964 as Reviewing Medical Officer and later occupied positions of increasing responsibility in the area of drug regulation, including acting Deputy Director and Director, Bureau of Medicine

In 1970 became Associate Commissioner for Medical Affairs and in this position was responsible for the early direction of the Office of Medical Devices which evolved into the Bureau of Medical Devices

As Associate Commissioner was responsible for international activities in the Commissioner's office

Served as chairman of the Research Involving Human Subjects Committee (RIHSC) from its formation in 1969 until leaving FDA

December, 1978 - Vice President, Medical Devices and Diagnostic Products, PMA

February, 198. - Vice President, Science and Technology, PMA

Mr. STETLER. Mr. Chairman, Mr. Volkmer, as you have indicated, I am currently the president of the Pharmaceutical Manufacturers Association. I'm accompanied today by Dr. Jennings, whom you've identified.

I'd like to say at the outset that we appreciate the opportunity, as others have indicated, to testify on this important subject of antibiotic use and bacteria resistance.

I might also say at the outset, at the risk of jeopardizing my brief remaining career at the PMA and jeopardizing Sidney Wolfe's rapport with his constituency, I agree with what he said about the effectiveness of your career as a Member of the House of Representatives. [Laughter.]

I, too, have enjoyed the opportunity to work with you, and I want to wish you the best of success in the U.S. Senate.

Mr. GORE. Thank you, sir.

Mr. STETLER. That just about sums up my areas of agreement with Dr. Wolfe. [Laughter.]

PMA represents 120 research-based pharmaceutical companies that develop and produce prescription medicines that are used in the United States and throughout the world. I think about 10 or 15 percent of those companies that are our members are involved in discovering, developing, and manufacturing antibiotics, which were

the first wonder drugs that are still among the most effective medicines that are available.

Recently there has been a considerable amount of discussion about the use of antibiotics and bacterial resistance. And certainly we would agree that antibiotic resistance does occur and it is a serious problem. But it would be a mistake in considering it to overlook, first, the enormous benefits that antibiotics have provided and are providing throughout the world in fighting infection and conquering diseases and, second, the suffering that they have relieved and the millions of lives they have saved and still continue to save.

Dr. Jennings, who has spent 15 years in private medical practice and 15 years with the Food and Drug Administration before joining our staff, will present the major part of our testimony. We have submitted it for the record, and he will summarize his comments, if he may.

Dr. JENNINGS. Mr. Chairman, Mr. Volkmer, I'd like to summarize briefly the statement we have submitted for the record.

I believe that any discussion of the use of antibiotics must begin with the recognition of the way that antibiotics revolutionized not only the practice of medicine, but indeed our whole way of life. Younger people cannot begin to appreciate how limited our medicine chests were before the advent of antibiotics. And I consider myself privileged to have been able to witness first hand the dawn of the antibiotic era.

I recall as a child many of my classmates bore the scars of the disfiguring mastoidectomy operation in which bone is chiseled away from behind the ear in order to eliminate the site of infection. Later, as an Army medical corpsman in the early 1940's, I witnessed our dependence on sulfa drugs, which were used by every route of administration for almost any kind of infection, with questionable results. As a medical student, I helped treat children dying of congestive heart faulure, today considered an affliction of old people, due to—in their case, due to rheumatic heart disease, a sequelae of streptococcal infection. At that time, pulmonary tuberculosis that had produced lung cavities was treated by collapsing the lung by removing part of the rib cage or by repeated injections of air into the chest. Other infections were treated in equally primitive and less than effective ways. And all of this changed virtually overnight with the advent of antibiotics.

Almost everyone is familiar with the story of Sir Alexander Flemming's recognition of an—the antibiotic properties of penicillin. Penicillin, however, was not used therapeutically until 1941, and in—and was in such short supply that some of the early patients who showed initial improvement died because not enough of the drug was available.

Under the pressure to meet wartime needs for this drug, a number of U.S. pharmaceutical firms launched a crash program to resolve complex technical and engineering problems in order to produce—mass produce it. And this began the transformation of the U.S. drug industry to its modern form and assured the rapid development and availability of subsequently discovered antibiotics. In addition to penicillin, antibiotics such as streptomycin, tetracycline and cephalosporins are probably the most important drugs

ever developed, and have dramatically shorted the length of many illnesses and saved millions of lives. The increased life expectancy in both the developed and less-developed nations can be attributed, at least in part, to the effective treatment of diseases such as tuberculosis, pneumonia, meningitis, syphilis, gonorrhea and rheumatic fever.

As antibiotics became generally available, the phenomenon of bacterial resistance was recognized. And it was brought out earlier, this probably antedated the human use of these weapons of chemical warfare among the micro-organisms. During all of this time, however, about 40 years, and after literally billions of doses of these drugs have been taken, bacterial resistance seems to be primarily a local phenomenon, dependent on the properties of the antibiotics used, the nature of the patients' infections—that is the micro-organisms involved—and their environments.

Now there's no doubt that resistance is a problem. However, the extent of the problem is unclear because many of the studies showing resistance are based on local—limited local clinical evidence. A recent comprehensive study by Atkinson and Lorian, referred to earlier, published in the October 1984 Journal of Clinical Microbiology, illustrates the point. This study analyzed the antibiotic response of nearly 6 million bacterial strains isolated from patients in 242 hospitals throughout the United States during a 12-year period. The bacterial strains were those that produce serious infections and have a relatively high death rate. The authors concluded that although local outbreaks of bacterial resistance do arise and many have serious consequences, bacterial susceptibility on a national scale has remained virtually unchanged during the last decade. And Dr. Parry, in reporting on his similar study, reached identical conclusions.

Now one reason the problem of bacterial resistance has been contained is the continuing development of new antibiotics. Since the introduction of penicillin, pharmaceutical companies have introduced new antibiotics at a rate of more than one a year, as shown by a list attached to our submitted statement of approximately 60 currently marketed antibiotics.

The pharmaceutical industry is confident that it can continue to develop new products that will help to deal with resistance. Drug companies are engaged in basic research on the mechanism of resistance and are developing new antimicrobials that will be less likely to induce resistance. A somewhat different approach was taken recently when an older antibiotic was given new efficacy against resistant pathogens by the addition of what might be called a decoy molecule to the compound. The decoy is destroyed by the bacterial enzyme that would normally destroy the antibiotic which is thus freed to kill the bacteria.

Pharmaceutical firms are also developing better diagnostic methods to enable physicians to determine more accurately and quickly the appropriate antibiotics to be used in particular cases. Dr. Kass referred to the need for this kind of research.

And I think it should be noted that, although one part of the clinical laboratory, clinical chemistry—that is, the determination of chemical components of the blood, such as blood sugar or cholesterol—has been automated. Microbiology, since we're speaking of

resistance, has until now resisted automation. However, we're confident that the research will develop methods that will prevent—will—will permit earlier identification of appropriate antibiotics to be used.

Now probably the most effective measures against antibiotic resistance are those taken at the local level. Clinicians must continue to increase their knowledge of the mechanics of resistance and of the proper use of different antibiotics. Most hospitals in the United States, partly at least to maintain accreditation, do carefully supervise the use of antibiotics so that resistance can be recognized early and appropriate steps taken. Our companies support and encourage these efforts which, in large part, have been responsible for the containment of this problem.

Mr. Chairman, that concludes our—my summary of our formal presentation, and——

[The prepared statements of Mr. Stetler and Dr. Jennings follow:]

STATEMENTS OF

C. JOSEPH STETLER AND JOHN JENNINGS, M.D.

ON BEHALF OF

THE PHARMACEUTICAL MANUFACTURERS ASSOCIATION

BEFORE THE

SCIENCE AND TECHNOLOGY

SUBCOMMITTEE ON

INVESTIGATIONS AND OVERSIGHT

ON

ANTIBIOTIC RESISTANCE

DECEMBER 19, 1984

STATEMENT OF C. JOSEPH STETLER
PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Mr. Chairman, I am C. Joseph Stetler, President of the Pharmaceutical Manufacturers Association. I am accompanied by Dr. John Jennings, PMA's Vice President for Science and Technology. We appreciate the opportunity to testify on the important subject of antibiotic use and bacterial resistance.

PMA represents 120 research-based pharmaceutical companies that develop and produce prescription medicines used in the United States and throughout the world. About 10 to 15 percent of our members are involved in discovering, developing and manufacturing antibiotics — the first "wonder drugs" that are still among the most effective medicines available.

Recently, there has been considerable discussion about the use of antibiotics and bacterial resistance. Certainly, antibiotic resistance does occur and is a serious problem, but it would be a mistake, in considering it, to overlook the enormous benefits that antibiotics have provided and are providing throughout the world in fighting infection and conquering disease, the suffering they have relieved and the millions of lives they have saved and will continue to save.

Dr. John Jennings, who spent 15 years in private medical practice and 15 years with FDA before joining our staff, will present the major part of our testimony. In addition to our remarks, Mr. Chairman, we would ask that our written statement be included as part of the hearing record.

STATEMENT OF JOHN JENNINGS
VICE PRESIDENT FOR SCIENCE AND TECHNOLOGY
PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Mr. Chairman, before proceeding further, I would like to describe briefly, from personal experience, what it was like before antibiotics were used in medical practice.

As a child, many of my playmates were required to have disfiguring mastoidectomy operations, in which bone was removed from behind the ear. Rheumatic heart disease caused by streptococcal infection was widespread, and hospital wards were filled with children dying of what we now consider a disease of old persons--congestive heart failure. As a medical corpsman in World War II, all we had was a handful of sulfas to treat infections--and they produced questionable results. In medical school, we treated pulmonary tuberculosis with what can only be described as mutilating operations to collapse the lung. These conditions changed virtually overnight following the development of antibiotics.

Younger people cannot begin to appreciate how limited our medicine chests were before the advent of antibiotics. Probably more than any other class of drugs, they revolutionized the practice of medicine and, indeed, our whole way of life. Physicians finally had medicines that were safe and actually effective in conquering disease.

Antibiotics truly have a special place in our history. The development of penicillin led to the creation of the modern pharmaceutical

industry--and ushered in a new therapeutic age.

Although penicillin had been discovered in 1928 by Sir Alexander Fleming, an English bacteriologist, it was not administered to a patient until 1941. The patient, who was suffering from blood poisoning following a shaving cut, quickly began to recover after he received the drug. But he died because the supply of penicillin ran out. The process of producing the drug was so complicated at that time that the world's supply was extremely limited.

A number of U.S. drug companies, however, launched a crash program to solve complex engineering and technical manufacturing problems to mass-produce the drug during World War II. With the large-scale production of penicillin to meet wartime needs, the pharmaceutical industry began to assume its modern form.

The introduction of penicillin also touched off an intense effort by drug companies to develop and produce other antibiotics, such as streptomycin, tetracyline and the cephalosporins. These and other antibiotics probably are the most important drugs ever developed, having drastically shortened the length of many illnesses and saved millions of lives.

During the past 45 years, these drugs have helped to cut dramatically mortality and morbidity rates from diseases such as tuberculosis,

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influenza, pneumonia, bronchitis, puerperal sepsis, urinary tract infections, meningococcal meningitis, syphilis, gonorrhoea, rheumatic fever, mastoid infection and osteomyelitis.

For example, the death rates in the U.S. from tuberculosis and influenza from 1950 through 1980 fell 96 percent and 72.4 percent, respectively.

In helping to conquer disease, antibiotics also have helped to increase life expectancy, which has increased in the U.S. by about 15 years since penicillin was first marketed. Major gains in life expectancy have also been recorded in recent years in developing countries, enabling them to accomplish in the 15-year period between 1950 and 1965 what had required about 70 years in Western Europe. Life expectancy in these countries, which was 40 years in 1950, increased to 50 years in 1965 and now is about 55 years.

According to an article by Sarah K. Brandel and Davidson R. Gwatkin in the May 1982 Scientific American, drugs and insecticides have made it possible to control many communicable diseases and appear to have been responsible for roughly half of the increase in life expectancy in developing countries.

As Mr. Stetler indicated, the use of antibiotics sometimes creates bacterial resistance. We have known about resistance almost since

antibiotics were first used. During all this time, after billions of doses of these drugs have been taken, bacterial resistance seems to be primarily a local phenomenon, dependent on the properties of the antibiotics used, the particular nature of the patients' infections and their environment.

There is no doubt that such resistance is a problem. However, the extent of the problem is unclear because many of the studies showing resistance are based on very limited local evidence. This was noted in a recent comprehensive study by Barbara A. Atkinson and Victor Lorian that was published in the October 1984 Journal of Clinical Microbiology.

The study was an analysis of the antibiotic response of 5,828,243 bacterial strains isolated from patients in 242 hospitals throughout the United States during a 12-year period. The bacterial strains were those that produce serious infections and a relatively high death rate.

The study--which encompassed 16 commonly-used antibiotics--showed that two species developed additional resistance to the drugs, but that six other species showed little change in susceptibility during the 12 years. "Although local outbreaks of bacterial resistance do arise and many have serious consequences, bacterial susceptibility on a national scale has remained virtually unchanged during the last decade," Atkinson and Lorian concluded.

One reason the spread of bacterial resistance has been contained is the

continuing development of new antibiotics.

Writing in the September 1980 Medical Times, Dr. James D. Hirsch, Dean of Graduate Studies at The Rockefeller University, stated: "For many years, it was feared that microorganisms would find ways to evade the action of these antimicrobial agents and that they would become resistant faster than new agents could be developed. Resistant forms did appear and this initial fear was reinforced but, in practice, the fear proved to be unfounded. New impressive antimicrobial agents are now emerging so rapidly that the physician can't keep up with them, much less the microbes!"

Since the introduction of penicillin, pharmaceutical companies have introduced new antibiotics at a rate of more than one a year, as shown by the attached list.

In a recent development, an older antibiotic was given new efficacy against resistant pathogens when a decoy molecule was added to the compound. The decoy agent--potassium clavulanate--is destroyed by the bacteria and thus the primary antibiotic is free to kill the bacteria.

The Food and Drug Administration approved a broad-spectrum antibiotic with potassium clavulanate in late 1984, and another antibiotic with this molecule is awaiting FDA approval. The decoy agent could be used to enhance the effectiveness of a wide variety of other penicillins and cephalosporins.

The pharmaceutical industry is confident it can continue to develop new products that will help to curb the spread of bacterial resistance. Drug companies are engaged in basic research on the mechanics of such resistance, and some of our companies are developing new antimicrobials that will be less likely to induce resistance. Pharmaceutical firms also are developing better diagnostic methods that will enable physicians to determine more accurately and quickly the appropriate antibiotics to be used in particular cases.

In addition, our companies are providing valuable scientific information to health-care providers to promote the proper use of antibiotics, in order to preserve their maximum efficacy.

Those at the local level also have a major role to play--which our companies will continue to support--in controlling the spread of bacterial resistance. Clinicians must learn the mechanics of resistance, they must become more knowledgeable about appropriate prescribing practices and they must ensure that the use of antibiotics is closely monitored so that, when resistance begins to spread, it can be recognized early and different antibiotics can be prescribed. In fact, most hospitals in the U.S., to maintain accreditation, do carefully supervise the use of antibiotics--which in large part explains why they have managed to control the spread of bacterial resistance.

Although the resistance problem may not be as serious as some people have feared, the pharmaceutical industry believes it is of major concern and deserves very close attention. At this time, much more data are needed to precisely identify patterns of optimum antibiotic use as well as the true extent of bacterial resistance.

Mr. Chairman, that concludes our formal presentation. Mr. Stetler and I will be happy to answer any questions you may have.

CURRENTLY MARKETED ANTIBIOTICS
INTRODUCED 1945-1984

YEAR MARKETED	ANTIBIOTIC	CLASSIFICATION
1945	Penicilin G Potassium	Penicillins
1946	Streptomycin	Aminoglycosides
1948	Bacitracin	Misc. Atibiotics
1949	Chloramphenicol	Chloramphenicol
1950	Oxytetracycline	Tetracyclines
1951	Neomycin	Aminoglycosides
1951	Polymyxin B	Misc. Antibiotics
1952	Erythromycin	Erythromycins
1953	Tetracycline	Tetracyclines
1954	Nystatin	Antifungal Antibiotics
1955	Penicillin V	Penicillins
1956	Novobiocin	Misc. Antibiotics
1956	Cycloserine	Antituberculosis Agents
1958	Kanamycin	Aminoglycosides
1958	Amphotericin B	Antifungal Antibiotics
1958	Troleandomycin	Misc. Antibiotics
1958	Vancomycin	Misc. Antibiotics
1959	Griseofulvin	Antifungal Antibiotics
1959	Demeclocycline	Tetracyclines
1960	Paromomycin	Aminoglycosides
1960	Methicillin	Penicillins
1961	Colistimethate/Colisin	Misc. Antibiotics
1962	Oxacillin	Penicillins
1963	Ampicillin	Penicillins
1964	Cephalothin	Cephalosporins
1964	Nafcillin	Penicillins
1965	Cloxacillin	Penicillins
1965	Lincomycin	Misc. Antibiotics
1966	Gentamicin	Aminoglycosides
1966	Methacycline	Tetracyclines
1967	Doxycycline	Tetracyclines
1968	Dicloxacillin	Penicillins
1970	Carbenicillin Disodium	Penicillins
1970	Clindamycin	Misc. Antibiotics
1971	Cephalexin	Cephalosporins
1971	Hetacillin	Penicillins
1971	Minocycline	Tetracyclines
1971	Spectinomycin	Misc. Antibiotics
1971	Capreomycin	Antituberculosis Agents
1971	Raifampin	Antituberculosis Agents
1972	Flucytosine	Antifungal Antibiotics
1973	Cefazolin	Cephalosporins
1974	Miconazole	Antifungal Antibiotics
1974	Amoxicillin	Penicillins
1974	Cephapirin	Cephalosporins
1974	Cephradine	Cephalosporins
1975	Tobramycin	Aminoglycosides
1976	Ticarcillin	Penicillins
1976	Amikacin	Aminoglycosides
1978	Cefadroxil	Cephalosporins
1978	Cefamandole	Cephalosporins
1978	Cefoxitin	Misc. B-Lactam Antibiotics

YEAR MARKETED	ANTIBIOTIC	CLASSIFICATION
1979	Cyclacillin	Penicillins
1979	Cefaclor	Cephalosporins
1981	Mezlocillin	Penicillins
1981	Bacampcillin	Penicillins
1981	Ketoconazole	Antifungal Antibiotics
1981	Cefotaxime	Cephalosporins
1981	Moxalactam	Misc. B-Lactam Antibiotics
1982	Piperacillin	Penicillins
1982	Cefoperazone	Cephalosporins
1982	Azlocillin	Penicillins
1983	Cefuroxime	Cephalosporins
1984	Amoxacillin/Potassium Clavulanate	Penicillins

Mr. Chairman, I'd like to summarize briefly the statement we have submitted for the record. I believe that any discussion of the use of antibiotics must begin with a recognition of the way antibiotics revolutionized not only the practice of medicine but indeed our whole way of life. Younger people cannot begin to appreciate how limited our medicine chests were before the advent of antibiotics. I consider myself privileged to have been able to witness first hand the dawn of the antibiotic era. I recall as a child many of my classmates bore the scars of the disfiguring mastoidectomy operation in which bone is chiseled away from behind the ear in order to eliminate the site of infection. Later, as an army medical corpsman in the early 1940s, I witnessed our dependence on sulfa drugs which were used by every route of administration for almost any kind of infection, with questionable results. As a medical student, I helped treat chidren dying of congestive heart failure, due to rheumatic heart disease. Today congestive heart failure is considered an affliction of old people. At that time, pulmonary tuberculosis that had produced lung cavities was treated by collapsing the lung by removing part of the rib cage or by repeated injections of air into the chest. Other infections were treated in equally primitive and less than effective ways. All of this changed virtually over night with the advent of antibiotics.

Almost everyone is familiar with the story of Sir Alexander Flemming's recognition of the antibiotic properties of penicillin. Penicillin, however, was not used therapeutically until 1941 and was in such short supply that some of the early patients who showed initial improvement died because not enough of the drug was available. Under the pressure to meet wartime needs for this ~~miracle~~ drug, a number of U.S. pharmaceutical firms launched a crash

program to solve complex technical and engineering problems in order to mass produce ~~the drug~~. This began the transformation of the U.S. drug industry to its modern form and assured the rapid development and availability of subsequently discovered antibiotics. Antibiotics such as streptomycin, tetracycline and cephalosporins are probably the most important drugs ever developed and have dramatically shortened the length of many illnesses and saved millions of lives. The increased life expectancy in both the developed and less developed nations can be attributed, in part at least, to the effective treatment of diseases such as tuberculosis, pneumonia, meningitis, syphilis, gonorrheae, and rheumatic fever.

As antibiotics became generally available, the phenonemon of bacterial resistance was recognized. During all of this time, about 40 years, and after literally billions of doses of these drugs have been taken, bacterial resistance seems to be primarily a local phenonemon, dependent on the properties of the antibiotics used, the nature of the patients' infections (that is, the microorganisms involved) and their invironments.

There is no doubt that resistance is a problem. However, the extent of the problem is unclear because many of the studies showing resistance are based on limited local clinical evidence. A recent comprehensive study by Atkinson and Lorian, published in the October, 1984 Journal of Clinical Microbiology illustrates that point. This study analyzed the antibiotic response of nearly six million bacterial strains isolated from patients in 242 hospitals throughout the United States during a twelve-year period. The bacterial strains were those that produce serious infections and have a relatively high death rate. The authors concluded that "although

local outbreaks of bacterial resistance do arise and many have serious consequences, bacterial susceptibility on a national scale has remained virtually unchanged during the last decade."

One reason the problem of bacterial resistance has been contained is the continuing development of new antibiotics. Since the introduction of penicillin, pharmaceutical companies have introduced new antibiotics at a rate of more than one a year, as shown by a list, attached to our submitted statement, of approximately sixty currently marketed antibiotics.

The pharmaceutical industry is confident that it can continue to develop new products that will help to deal with resistance. Drug companies are engaged in basic research on the mechanisms of resistance and some are developing new antimicrobials that will be less likely to induce resistance. A somewhat different approach was taken recently when an older antibiotic was given new efficacy against resistant pathogen by the addition of a decoy molecule to the compound. The decoy is destroyed by the bacterial enzyme that would normally destroy the antibiotic which is thus freed to kill the bacteria.

Pharmaceutical firms are also developing better diagnostic methods to enable physicians to determine more accurately and quickly the appropriate antibiotics to be used in particular cases.

Probably the most effective measures against antibiotic resistance are those taken at the local level. Clinicians must continue to increase their knowledge of the mechanics of resistance and the proper use of different antibiotics. Most hospitals in the

United States, partly, at least, to maintain accreditation, do carefully supervise the use of antibiotics so that resistance can be recognized early and appropriate steps taken. Our companies support and encourage these efforts, which, in large part, have been responsible for the containment of the problem.

Mr. Chairman, that concludes our formal presentation. Mr. Stetler and I will be happy to answer anyquestions you may have.

Mr. GORE. Dr. Jennings or Mr. Stetler, whichever one of you wishes to respond, these statistics provided by Dr. Wolfe seem to be very troubling. Would you agree that the figures he has provided on—on chloramphenicol, for example, are troubling?

Mr. STETLER. I think you have to say they're troubling. Some of the figures in the—in the statement presented by Dr. Wolfe, which I have just seen a couple a moments ago, I think, you know, bears some careful scrutiny and analysis. One particularly that strikes me is—these statistics on increasing prescribing of antibiotics.

I've no doubt—I don't question the accuracy of the extent of the increase in the prescribing. I think there has to be a variety of reasons for the increase in prescribing. To automatically label that chart as misprescribing, I think, is an overstatement and an overreaction. Increases in the population around the world, increases in the number of antibiotics that are available, increased availability of these products in various parts of the world have got to be factors in terms of the increase in the number.

Still, I wouldn't try to defend that all of that increase is proper. I'm sure some of it is not. But it's—it's a matter of bringing it into proper focus, I believe.

Mr. GORE. Well, let's look at the specific examples. In 1983, almost a half a million prescriptions for chloramphenicol, and half of them, 220,000, were for indications for which the drug is clearly not indicated, such as tonsillitis and to prevent infection after surgery.

Mr. VOLKMER. Mr. Chairman?

Mr. GORE. Yes.

Mr. VOLKMER. Could I interject once more on this? I'd just like to ask a question in regard to——

Mr. GORE. I—do you have to leave or something?

Mr. VOLKMER. No.

Well, I can do it afterward, but I thought it would be advantageous to find out first on the methodology of doing this and how this was determined, these facts and figures were determined.

Mr. GORE. Oh, I'd be glad to ask that.

Mr. VOLKMER. That's the only thing I'm interested in——

Mr. GORE. Sure.

Mr. VOLKMER [continuing]. Right now.

Dr. WOLFE. This is data that is really collected—it's collected by a company called IMS in Ambler, PA, and it is the standard data

used mainly by the drug industry to look at the number of prescriptions that are written by doctors. It's a nationwide sample representing all geographic areas and all subspecialties as to how many prescriptions they're writing and what they're writing them for. I—I think that it is widely enough used. I'm sure there are some minor methodologic problems, but it's the best source, I think, right now, in terms of looking in the doctor's office or elsewhere where the doctor's prescribing and seeing what——

Mr. GORE. This is the National Disease, the Therapeutic Index?

Dr. WOLFE. The National Disease and Therapeutic Index.

Mr. GORE. You're familiar with that, aren't you, Dr. Jennings?

Dr. JENNINGS. Yes; we're—we know about it.

Mr. GORE. Yeah.

Mr. VOLKMER. Well, could I ask—well, go ahead, and then I'll ask.

Mr. GORE. Thank you.

Half of the prescriptions, a quarter of a million prescriptions, for chloramphenicol were for indications for which the drug is clearly not indicated. Now that—that—that's a serious problem, isn't it?

Mr. STETLER. It certainly is.

It possibly could be—and I've no quarrel with the source of this data. We use IMS all the time and respect this data. As I look at that chart, the only thing that possibly might occur to me is that maybe there are multiple reasons or maybe the patient is suffering from multiple ailments that would justify some of that, but I would be at a loss right now at this moment to—to be able to comment very effectively on that. I'll take a look at it and——

Mr. GORE. Now which company makes that?

Mr. STETLER. Parke Davis.

Mr. GORE. Parke Davis. Now is it—would—would it be fair to expect that they——

Mr. STETLER. That is one of our major membership.

Mr. GORE. In your membership?

Mr. STETLER. Yeah.

Mr. GORE. Would it be fair to assume that they have people going around to doctors, the detail people, encouraging the use of chloramphenicol?

Mr. STETLER. No; I think it would not be fair to assume that.

Dr. WOLFE. I would agree with that, at least now. I think earlier on when it first came on the market, it was used and there were recommendations for use for a much greater scope of indications. And, unfortunately, as I mentioned, in the case of the lincomycin, the—the bad habits that are inculcated, either out of ignorance or out of malice by some drug detail people, can last long after the encouragement is gone. I would agree with Mr. Stetler that it's unlikely that any drug detail person is now encouraging any of these kinds of uses. And they've gone down somewhat, but they still are at an, I think, alarming high level.

Mr. GORE. Well, which raises the question of how to—how to—how to stop that. And I guess what I—what I—what I'm getting at is—is whether or not the industry has some responsibility, having encouraged its use in the past, to actively disseminate information to the physicians about the newly recognized contraindications.

Mr. STETLER. First of all, the industry does disseminate information, and is doing it currently. Again, there may have been some culpability initially. To the extent of it, I wouldn't agree to the extremes that Dr. Wolfe would go, but certainly that has been terminated.

I have no doubt there are some residual misprescribing habits that may exist from wherever they got their original perceptions as the way the drug should be used. I don't think a Government-funded contrived counter-detailing system has anything to justify it.

However, I think there's some—some effectiveness that was—would come out of the type of a program that Dr. Schaffner described in Tennessee. It's a program where doctors are visited by their colleagues. I think that is an effective approach. I think, as has been stated before, to the extent that misprescribing exists, one of the very effective ways is better education. Now that can't just start and stop in the medical schools, it has to be carried on to doctors who are now in practice. And I think the Tennessee type of program is a good one. That program and others have identified what we might call bad prescribers.

Mr. GORE. Would—would PMA be willing to consider funding some programs of this kind? I don't ask that in a—in a joking way. I'm serious.

Mr. STETLER. Having just been revisited, the PMA, and been accommodated with a $1.8 million shortfall, I'm not looking for new programs to fund. And it should probably not be funded by the PMA. But there are prospects that individual companies or the industry in general might consider that. I don't know, maybe they're even participating in the Tennessee program. I have—I have no knowledge.

Dr. WOLFE. Government funded.

Mr. STETLER. What's that?

Dr. WOLFE. Government funded in Tennessee.

Mr. GORE. He says the Tennessee program's Government funded.

Tetracyclines in 1983, 129,000 prescriptions written for children 9 or less, 129,000 children that are going to have these stained teeth and—and other pro—temporary bone growth loss. But that's—I guess that's the major problem with it.

How do we get the information to them? Is it—having promoted this usage, is it fair to just say that—that it's—it's up to the medical profession to—to—to catch up with the latest data?

Mr. STETLER. No. And I'm not saying that. As I said, too, our companies are busy all the time disseminating information. We've been very much the funders of the program of the American Medical Association and the National Association of Retail Druggists NARD in putting out inserts for patients, patient inserts. A lot is going on. More could go on.

But I still think to the extent they can identify that many prescriptions, and if you could identify the source of it, and if that is bad medical practice, then maybe we could do a better job of dealing with the people that are perpetuating the bad practices. It's not probably an educational process needed for the whole medical profession.

Mr. GORE. Yeah.

Mr. STETLER. Maybe we could have more of a rifle approach in terms of our educational effort.

Mr. GORE. Dr. Schaffner, your experience would indicate that's an effective way to attack the problem, wouldn't it?

Dr. SCHAFFNER. Oh, far and away, the most effective way, yes.

Mr. GORE. How would you do that on a nationwide basis? Is your main problem confidentiality?

Dr. SCHAFFNER. I think confidentiality in both patients and physicians is important. But there are any number of—I don't—I don't have a panacea—but there are any number of sponsored programs, whether they be in health maintenance organizations and the like in the private sector, or Medicaid/Medicare in the public sector, where use of antimicrobials could be reviewed on a systematic basis, and you might not cover 100 percent of the problem, but you sure could get a large proportion.

Mr. GORE. What was the cost of the Tennessee experiment?

Dr. SCHAFFNER. Well, it was an experiment. We were doing it for the first time. And my memory is that we had a 4-year grant for about three-quarters of a million dollars.

Mr. GORE. Uh-huh.

Dr. SCHAFFNER. Obviously, when you put things on line and make them more routine, you get enormous cost savings.

Mr. GORE. Yeah.

Dr. SCHAFFNER. There are—both Drs. Avorn and Soumerai—and we have done some, theirs more elaborate, ours more quick and dirty cost-benefit surveys, and it looks as though you save more money in reducing prescribing than you spend in instituting the program.

Mr. GORE. Yeah. So—so it's a cost saver in the—in the long run.

Dr. SCHAFFNER. Yeah. Jerry pushes——

Mr. GORE. Probably.

Dr. SCHAFFNER. Jerry pushes that harder than we do.

Mr. GORE. Yes.

So—so it is feasible to target those physicians who are misprescribing specific antibiotics and rifle-shot education for them on the particular mistakes they're making?

Dr. SCHAFFNER. I believe that's a much more effective way to do it than to try to reach everyone. Even in our meticulous approach, we, on occasion—our net caught some physicians who had not been prescribers, through a glitch in the computer run or something.

Mr. GORE. Like the——

Dr. SCHAFFNER. And they immediately say, why are you talking to me? I don't use this drug. And so you don't need to reach those folks.

Mr. GORE. Yes. Yes.

Well, we should—we ought to do that, shouldn't we, nationwide?

Dr. SCHAFFNER. I think we ought to do it certainly, gradually. And I—I don't know that we're in a position to, you know, to introduce a nationwide program, but I think, increasingly, we could scale it up and test it further——

Mr. GORE. Yeah.

Dr. SCHAFFNER [continuing]. And demonstrate that it works and, in a gradual way, in——

Mr. GORE. But that ought to be——

Dr. SCHAFFNER [continuing]. Collaboration with the industry——

Mr. GORE. That ought to be our objective.

Dr. SCHAFFNER [continuing]. Government. Sure, I think so.

Mr. GORE. Yeah.

Where the common cold is concerned, the—the figures that Dr. Wolfe has given us indicate—where are those figures—51 percent of the people with the common cold were given antibiotics. That's—that's not only an unnecessary expense, unnecessary risk in some cases, depending on the antibiotic, but it's also a direct contribution to the problem of—of promoting resistance genes, isn't it?

Dr. Kass, you're shaking your head.

Dr. KASS. Yes, sir; I'm shaking my head. I think your first two groups of questions isolated areas in which there is clear excess, and I think we're of a whole. In fact, the community is—is—is pretty much united about the problem of tetracycline in children and chloramphenicol used in general.

Mr. GORE. Lincocin also?

Dr. KASS. I'm sorry?

Mr. GORE. Lincocin also?

Dr. KASS. Well, that—that's a separate question. Let me try to address the cold problem——

Mr. GORE. Yes, please do.

Dr. KASS [continuing]. Because you raised that initially.

One of the questions we have to ask is why do clinicians, therefore, use antibiotics so widely in treating common colds, and they're——

Mr. GORE. They don't know whether it's viral or bacterial.

Dr. KASS. Well, No. 1, a small percentage are bacterial, and it's very difficult without expensive tests to determine which is streptococcal.

No. 2, and I think this has to be stressed very hard, our ignorance about the common cold is still enormous. And I would give as an example a recent study completed by my colleague, Dr. Komeroff, on simple sore throat, and people coming into an ambulatory clinic, in which 20 percent of them were found to be associated with antibody rises to Chlamydia an organism that we paid no attention to in the past, that now looks like we better pay attention to. Now Chlamydia happens to be susceptible to erythromycin, and it turns out that in 20 percent of these simple sore throats, where ordinarily we say this is due to a virus and it's perfectly silly to use antibiotics, except we might culture, and so on, it turns out that, in fact, considerable relief has been afforded to these patients.

I would just want to point out a third factor in here. It doesn't take much of a look and much of a memory to see the virtual disappearance of mastoiditis, of severe ear injuries, and so on. Now I think we would all agree that a very substantial segment of this is due to the use of antibiotics. And we now have increasing information that the rate at which middle ear infections, which have common complications, bacterial complication of viral disease of the nose and throat, that the rate at which these appear is also very beneficially affected by the prompt and early use of antimicrobial drugs.

So we're simultaneously preventing severe complications due to bacteria. We're treating a certain number of infections that were due to organisms that we haven't recognized until very recently. And I think this is why a lot of clinicians are saying, look, you fellows can tell us all you want. I know my patients do better. The fact of the matter is they've been right in a certain number of instances. Now we have a new problem of trying to figure out when you can pinpoint. Can you use a rifle here or do you have to use a shotgun? Right now I don't think anyone knows how to use a rifle except by very expensive and absolutely inappropriate laboratory tests, not close to ready for mass use.

Mr. GORE. Dr. Wolfe?

Dr. WOLFE. Well, I think that when the figure is 51 percent and it is not some small fraction of people with common colds who might have some specific suspicion of bacterial infection, but a large proportion, I think that it is really cause for alarm. And when one sees that one of the more commonly prescribed antibiotics, or cephalosporins, which even on the Chlamydia theory would not be at all advisable, one thinks that it is more of a blind kind of approach to the cold than anything terribly rational. And, again, it's gone on for a long time. It's better than it used to be—not much, I'm afraid—and it predates the—the notion that Chlamydia might be concomitant in people with a cold.

But I think—I think that the magnitude of 51 percent of all people who walk into the doctor's office for whom the doctor makes—the doctor makes the diagnosis for the common cold—get antibiotics is still way too high and is, I think, an example—you may not think it's as clear as the examples of tetracycline or chloramphenicol—but I think another example of misprescribing.

Mr. GORE. Dr. Jennings, you—do you want to comment on this?

Dr. JENNINGS. I agree with Dr. Kass that you have to consider some of the effects of antibiotic therapy in the past.

But more to the point, in a nation of 220 million people, there are certainly more than 3 million common colds a year. And what moves a person to go to the doctor with his cold, I think it's because he feels that there's something more than a common cold. And perhaps what we ought to be encouraged by is that 50 percent of the time the doctor has the courage not to prescribe an antibiotic. [Laughter.]

These patients tend, I would think, to be people who have some health concern. They may be elderly patients or children. Most otherwise healthy adults treat their common colds not by a visit to a physician.

Mr. GORE. Dr. Wolfe?

Dr. WOLFE. Well, just two responses.

First of all, there is, if anything, perhaps a misrepresentation with fewer elderly people in this group, which is broken down by age as well, than you'd expect. Second, I think one of the reasons why this subset—I mean, obviously, it isn't the complete number of people who get common colds—why this 3.3 million people go to the doctor when they have a cold is in order to get an antibiotic. And the reason that that happens is not, as is often the case, to be blamed on the patient, but it's to be blamed on the practice of medicine such as it is for those people who have made the connection,

common cold, shot of penicillin or dose of cephalosporins, or whatever. Once that information gets out in the community, there are those people who believe they have a right—in fact, they're going to suffer if they do not go to the doctor and get a prescription. And—and I'm glad—as Dr. Jennings phrases it, that half the doctors resist this. But the origin is not the patient. Patients are not born into this world with the view that antibiotics are required for common colds. It is learned from their friends who learned it from their doctors when they went, and so forth, and from the indiscriminate promotion of a lot of antibiotics for upper respiratory infections, more in the past than now.

So I think that one of the main reasons why I think a lot of people do go to the doctor for a common cold is in order to get an antibiotic, and half of the time they're satisfied.

Mr. GORE. Mr. Volkmer.

Mr. VOLKMER. Yes, I have several. One is that I'd like to address the question—Dr. Jennings, in your statement that the basic pharmaceutical industry is confident in continuing to develop new products to help curb the spread of bacterial resistance, in that line do the pharmaceutical industry, the various houses, are they constantly keeping track of all the bacteria resistance and also the effectiveness, the efficacy, of the drugs, et cetera?

Dr. JENNINGS. Yes, sir. We're obviously very concerned with the resistance as a problem in the use of currently available antibiotics. It's been said earlier that resistance is probably the single greatest stimulus for the production of a new antibiotic. I'm not sure of that. But that is an important concern to us. And, as I indicated, there is research, not only on improving the currently available families of antibiotics, but in novel approaches such as the one that will rejuvenate some of the older antibiotics that are—that show a resistance because of the presence of a bacterial enzyme. And the development of a single new molecule that, in effect, deactivates that enzyme promises that some of these older and very useful and relatively nontoxic antibiotics will be useful again.

Mr. VOLKMER. How long do you basically have to test the new drugs before you put them on the market?

Dr. JENNINGS. That's a subject that receives a lot of attention. The numbers keep going up, but currently it's generally stated that for the average drug it takes perhaps 10 years from the earliest research on the compound to FDA approval. And this can cost up to $70 or $80 million. Antibiotics may be somewhat different because they tend to be a succession of relatively closely related compounds and, to some extent, the screening for activity is much more precise than it is with other kinds of drugs.

Mr. VOLKMER. We now have an antibiotic—for the first time we're using a decoy——

Dr. JENNINGS. Yes.

Mr. VOLKMER [continuing]. Basically with it. Well, could we anticipate we will see more of that type of——

Dr. JENNINGS. I think so, and more drugs, whether they are primarily antibiotics or they accompany the use of antibiotics, that go to the heart of the problem, the plasmid activity, the transference and development of resistance in that way.

Mr. VOLKMER. In other words, something to either decoy the resistant gene or to first perhaps destroy that resistant gene before?

Dr. JENNINGS. To prevent the gene from doing its work, which is production either of a mechanism against the antibiotic—the enzyme is one example—or, in some instances, the organism modifies its own cellular structure. The cell membrane is strengthened to prevent the penetration of the antibiotic. And so there is some hope that, through basic research, as was alluded to earlier, these mechanisms will become much more clear to us and drugs can be developed that will obviate the development of resistance, or at least lessen it to a great extent.

Mr. VOLKMER. Dr. Wolfe, as one who has used the physicians and the medical profession in many times for a period of my life, I'd like to ask you a little question. If I had come to you and you're a practicing physician, and I have a cold, but I also have a very sore throat and you examine it and it's very red, and I'm running a temperature of about 101 or 102, would you prescribe an antibiotic?

Dr. WOLFE. Well, let's assume you didn't have a past history of rheumatic fever or rheumatic heart disease, whatever, and you came in, I would—if your throat looked like one that might have—that might be a strep throat, I would certainly do a throat culture and, on the outcome of that, if it were positive for group A beta-hemolytic strep, would write you a prescription for penicillin, assuming you weren't allergic to it, and, if you were, for erythromycin.

So I think that there are instances where people who have a cold and a sore throat might later turn out to need a prescription for an antibiotic. It turns out, though, that, as you probably know, most—the majority of sore throats, particularly those that are associated with a cold and are likely a consequence of a cold, are not bacterial, they're viral sore throats and do not need such treatment.

If someone came in without a cold at all with the isolated finding of a temperature and a red sore throat and puss in the tonsil or crypts—if they were one of the few people that still have their tonsils left—that might be a more likely circumstance where an antibiotic would get prescribed and a throat culture. Still that person would not have the diagnosis of a common cold, they'd just have a sore throat.

Mr. VOLKMER. Now, then, I'm a physician in a small town in a rural area and, you know, it's going to take me maybe until tomorrow to get the report back from the pathologist.

Dr. WOLFE. Well, in the case of—remember the—the only reason that we give antibiotics for sore throats is to prevent the consequences, which are rheumatic fever, rheumatic heart disease, and so forth. The waiting of one day has little, if any, impact on the prevention of rheumatic fever or rheumatic heart disease. It has even less impact, if the sore throat's been around for a couple days, on the actual course of the sore throat. Now you are not treating the acute illness, you're preventing something in the future. Waiting a day or even two days is not going to make really very much difference, particularly when the likelihood is that it will not be group A beta-hemolytic strep and will, therefore, not need any antibiotic.

Mr. VOLKMER. Well, let's see. You're the same physician who just read about his fellow practitioner being sued for $1 million or something. No different answer—or 5 million.

Dr. WOLFE. The former president of the AMA has recently said that 95 percent of malpractice is from practicing bad medicine, not from shenanigans of the——

Mr. VOLKMER. I agree. I agree.

Dr. WOLFE [continuing]. Lawyers or insurance companies. And I think that the——

Mr. VOLKMER. What I'm trying to get at is this, Dr. Wolfe, whether you may or may not agree, that perhaps some of the excess use of antibiotics may be related to the fear of the physician of not covering all the bases.

Dr. WOLFE. It might be, but I think that the other side of the coin is that the physician who misprescribes an antibiotic for an uncomplicated common cold and whose patient gets aplastic anemia if it was chloramphenicol, or colitis if it was clindamycin, or an anaphylactic reaction from penicillin, if it was penicillin, also should worry about the malpractice from the prescribing. And I think that those might tend to offset one another, I would hope.

Mr. VOLKMER. I won't disagree with that, but I'm just trying to say put yourself sometimes in the clothes of the physician that's out there doing it.

Dr. Kass, you were a member of the—I don't know, were or still are, I don't know—a member of the National Research Council of the National Academy of Sciences?

Dr. KASS. Of the committee on——

Mr. VOLKMER. On the committee of the—right.

Dr. KASS. Yes, sir.

Mr. VOLKMER. I noticed in your paper that you had not come to the same conclusion as Dr. Wolfe has done as far as the subtherapeutic use of antibiotics and as far as proposals by the FDA.

Dr. KASS. Yes, sir; not only I, but the entire committee.

Mr. VOLKMER. Pardon?

Dr. KASS. Not only I, but the entire committee came to a different conclusion from Dr. Wolfe's.

Mr. VOLKMER. And did you not recommend additional studies and tests being——

Dr. KASS. We did.

Mr. VOLKMER. Have all those been done?

Dr. KASS. No. Two are in progress. I don't know about the other two. I only know if two of the four that we recommended that are in progress.

Mr. VOLKMER. Do you know if a study is being done or tests being done by the Animal Research Institute?

Dr. KASS. I know of some. I don't know which one you have in mind.

Mr. VOLKMER. Well, the one in regard to the epidemiology of examining subtherapeutic use of antibiotics in animals in relationship to having disease resistant or bacteria resistance in animals and humans.

Dr. KASS. Well, there're many such studies that have been done that go on, yes. It's a huge amount of literature here.

Mr. VOLKMER. Will those be helpful in making the determination?

Dr. KASS. Well, if—if you're referring to the one that's out in Seattle now, I don't think it will be helpful.

Mr. VOLKMER. All right.

What areas do you think that need to be studied, and the committee, need to be studied before a determination can be made?

Dr. KASS. Well, I—I—I despair that we're under the present circumstances ever going to be able strictly to separate subtherapeutic from therapeutic use of drugs in terms of their effects. I cannot conceive of any study that will separate these in the existing conditions.

Mr. VOLKMER. Is that because you're going to continue to have therapeutic use of the same type of medications, et cetera?

Dr. KASS. Not only will we have therapeutic use—which I don't think we can deny any farmer unless we're ready to subsidize him for any losses while we do the experiment, which would be very considerable—but also because even if you move animals to a farm where no antibiotics are being used and given feed that has no antibiotics, it takes years before those resistant bacteria disappear. So even—even to get animals that don't have resistant bacteria would require a technology that would take many years to develop and an enormous expense. I just don't see it in the cards.

May I make a comment about the question you put up to Dr. Wolfe also——

Mr. VOLKMER. Yes.

Dr. KASS [continuing]. Mr. Volkmer? Because I think here also perhaps I would treat you a little differently from—I'm not trying to take patients away from Dr. Wolfe, you understand, but I think I would go out a little differently, and the reason is something that we ought to be paying more attention to.

He's absolutely right about the rheumatic fever story. We know that rheumatic fever has always been socioeconomically linked, and that most of it, to this day, occurs in people who are overcrowded and tend to be in lower socioeconomic conditions. And for someone like yourself coming in, the fear of rheumatic fever would be pretty tiny. And the idea of using a culture would have certain economic disadvantages given that the cost of the culture is usually as great as the cost of visiting the doctor. It wouldn't be nearly as necessary.

What has been overlooked in recent times have been the complications of colds, particularly in children where most of the colds are treated by doctors. People haven't paid enough attention to the problem of middle ear infection, which now has been demonstrated not only to be extremely common in youngsters with colds, but also those who've had middle ear infection turn out to have higher rates of impaired hearing and, maybe because of this, lower IQ's when they're in school. The consequences of this are very difficult to chart in exact terms, but they're obviously highly undesirable.

There's no question at all that the early and prompt use of antimicrobial drugs prevents a good share of this complication from occurring, and equally no question that, when the complication's been diagnosed, it must be treated very vigorously and—and—and very precisely. I think this is going to be a much more important

reason why doctors are going to use antibiotics in—in people's sore throats than the rheumatic fever problem, at least in our community, in—in well-off America.

There's another side to this. For those of us who are on the firing line and have to make the kind of decision you're concerned with. There's a great deal of data now to show that if we treat the family member with a sore throat and we look at where rheumatic fever does occur, even in high-risk people, it's the youngster who's a sibling who never got sick who's most likely to have rheumatic fever now. A lot of studies are showing this. The case for even treating every member of the family, every close contact, in order to prevent rheumatic fever in a real susceptible is overwhelmingly large. Now a lot would say, that's absolutely abhorrent to go in and dose everybody in the family with a drug when you've got one susceptible, but if you start to examine the consequences of rheumatic fever showing up in a member of the family who is never sick, there's no question which way my line would go.

Dr. WOLFE. This all precludes—this all—this all assumes that you've already made one diagnosis though. You're not talking about——

Dr. KASS. No.

Dr. WOLFE [continuing]. Just coming in with a cold——

Dr. KASS. No. No.

Dr. WOLFE [continuing]. Or have a——

Dr. KASS. No. No.

Dr. WOLFE [continuing]. Strep throat.

Dr. KASS. No. Let—let me tell you what the data are. If—if you—and this has been repeated over and over again. If you go in to a high-risk family and treat a sore throat in the symptomatic person and don't treat the rest of the family and look for where rheumatic fever has occurred—you haven't done cultures you don't——

Dr. WOLFE. I understand that. But you're at least—you have one target individual who you suspect has the——

Dr. KASS. Who—who—who has the suspect—suspected streptococcal throat. It turns out that these days, because the treatment is so effective, the risk occurs in the people who never got sick and, therefore, never got treated. And that's not to be taken lightly. So, in fact, there's a case for treating more, not less, as far as I'm concerned.

Dr. WOLFE. Sore throats but not colds.

Dr. KASS. Well, yeah. Well, the trouble is so many colds are tied up with sore throats and so many people——

Mr. VOLKMER. Which—which—which——

Dr. KASS. It's a very tricky question.

Mr. VOLKMER. Which means if that it, that may explain to some degree the increased use of antibiotics, not only populations exposed, but other reasons for using antibiotics. I'm not—not——

Dr. KASS. Yes.

Mr. VOLKMER [continuing]. Dr. Wolfe, that there may be excess of use of antibiotics. I won't deny that. I don't think anybody denies that. But that may explain some of the——

Dr. KASS. Well, it—it certainly has changed my practice. I used to give people a nice long talk about how it was a waste of time and I exposed them to needless expense and needless infection

and—and—and needless side effects from the drug. You don't treat colds with antibiotics. And I've taught this for years to the students, and I just don't teach it anymore.

Mr. VOLKMER. In other words, what you're telling me is that if we deny—let's say there was a legislative prohibition that you—you're going to tell a doctor that you're not going to use antibiotics for the treatment of a common cold. Are you telling us there's a possibility that he may see an increase in—in a—in an inner ear infection, middle ear infection?

Dr. KASS. I've no doubt of it. And I—and I certainly would expect to see mastoids start coming back and things of this sort.

Mr. VOLKMER. Doctors, what are the—again, as one trying to learn—what would be the treatment for salmonellosis, salmonella, normal treatment? Anybody that's ever treated it.

Dr. WOLFE. You're asking——

Dr. KASS. Which one of us are you asking?

Mr. VOLKMER. Any—all of you, I don't care.

Dr. KASS. There—there is no effective treatment for salmonellosis fundamentally. What antibiotics have—will do in people with severe bloodstream spread is reduce that risk. But getting rid of salmonella by antibiotics has been a complete failure. It's a preventive problem, not a treatment problem.

Mr. VOLKMER. Just what, telling you to be quiet and maybe—do you have to take, say, water or liquids.

Dr. KASS. Well, if you treat it, you treat the diarrhea.

Mr. VOLKMER. Right.

Dr. KASS. You can treat that. You can treat the symptoms that the patient has and make them much more comfortable, but you cannot—but at least current day antibiotic treatment does not help get rid of salmonella any faster than Mother Nature does it without such help.

Mr. VOLKMER. I have no further questions.

Mr. GORE. I asked other witnesses yesterday about contracts or research grants with entities in—interested in this question. Perhaps it's only relevant to the academic members. But, Dr. Kass, I believe you do have a major project with the pharmaceutical companies consortium that is working on this subtherapeutic drug.

Dr. KASS. Yes. I wouldn't say major, but our laboratory spends about $5½ million a year, and this one is for about $100,000. I think we can get along without it, but we——

Mr. GORE. Yeah.

Dr. KASS [continuing]. Chose to—the reason being that when our committee met and tried to brainstorm quest—the answers to the questions of the type that Mr. Volkmer posed, which was how to get to the bottom of this, among the possible approaches that were offered were two, one that came from me and one that came from one of the other members of the committee. The one from me, since I've been interested in urinary infections, was to look at the incidence of—and the prevalence of—of unsuspected infection of the urinary tract in workers, since they're mostly female personnel—workers in the chicken abattoirs where they have an enormous exposure all day long to whatever the bacteria are that are in the chickens, and we know that there's a high rate of resistance in such chickens.

And the second was—a question arose whether strict vegetarians would be more or less likely than meat eaters to have antibiotic resistant bacteria in their feces. The question about vegetarians came back to me because my colleague, Dr. Sacks, and I have been studying macrobiotic vegetarians in terms of their cardiovascular risk factors. They happen to have unusually low cholesterols, and so on, which has been of great interest to us. And since we had access to such people, the question arose, could we determine whether the—such strict vegetarians compared with neighborhood controls of the same age and sex who eat meat at least three times a week, whether their stool flora would be different in terms of the incidence of antibiotic resistance. And since we're equipped to do that type of study and are doing something similar to it for other reasons, it seemed reasonable.

It seemed reasonable to me also—and I suggested this at the time, that since there is a very large number of Seventh Day Adventists out in the Los Angeles area and there's a what used to be the College of Medical Evangelists, Loma Linda University, where the head of infection happens to be a—a—an old friend, a former trainee with me, that it might be useful also to look at such people because they eat dairy products but eat no meat. And so this study is simultaneously going on in Loma Linda and in Boston to see whether two types of vegetarians—strict ones who eat no dairy products, vegetarians who eat no meat but eat vegetarian products—they eat dairy products—have different resistant bacteria than the ones who eat meat.

In terms of the women with urinary infection working in the assembly line in the chicken factories—I gave you some of the preliminary data—my only point here is that this is being financed by the Animal Health Institute. Yes; not as a contract, but as a research grant. The money comes into our university and is dispensed from the university. There is no direct relationship any more than any other——

Mr. GORE. I'm not—I'm not——

Dr. KASS [continuing]. Grant that comes in.

Mr. GORE [continuing]. Not—not drawing any inferences——

Dr. KASS. But I—I think that ought to be made clear.

Mr. GORE. I—I—over the years, we'd just like to have that stuff for the record. And, Dr. Schaffner, you don't have——

Dr. SCHAFFNER. Just from the National Center for Health Services Research.

Mr. GORE. All right.

Dr. WOLFE. We don't get any money from the drug industry, you'll—you'll be happy to hear. [Laughter.]

Mr. STETLER. Mr. Chairman?

Dr. WOLFE. To their regret.

Mr. STETLER. Obviously my entire income and Dr. Jennings' comes from the pharmaceutical industry. I'm sure there's no implication here that our testimony is less accurate, honest or anything else.

Mr. GORE. No, no, no. Totally objective, I can tell.

Mr. VOLKMER. Mr. Chairman?

Mr. GORE. Yes.

Mr. VOLKMER. I have a question.

Mr. GORE. No, we need to wrap it up though.

Mr. VOLKMER. Yeah, I know. I'd like to ask a quick one of Dr. Kass. As a—as a result of serving on the committee and perhaps the background that you have in the past and the use—go back to the use of subtherapeutic antibiotics in animals, do you find that they're used not only for growth purposes, but also for disease resistance and prevention?

Dr. KASS. Oh, yes, there's no question about the rate. The rate of diarrhea is very much lower. The rate of hoof rot and liver abscess is lower in those that get subtherapeutic amounts of drugs.

Mr. VOLKMER. Yeah.

Dr. KASS. But I have to add the proviso that there's so much therapeutic use in these herds that we can't be entirely sure that it's due only to the subtherapeutic amount of drug.

Mr. VOLKMER. I—I—I agree, but I mean there's been some implication that it's basically used for a growth factor, but the fact that it does reduce—reduce disease, et cetera, does permit better growth also.

Dr. KASS. No que—no doubt of that.

Mr. VOLKMER. Let's go back just quick, Mr. Chairman, to the—let's say the poultry industry, and the way flocks are today, especially broilers, are done. If you had what we call a common cold—we go back to that good old common cold—and you had no subtherapeutic antibiotics in the feed and a few of those broilers got that little common cold, what would that broiler person do?

Dr. KASS. Oh, we know exactly, because we've gone to farms and talked to farmers and have done this in Great Britain as well. I was on sabbatical in London during some of these things, and I did some firsthand—there's just no question. If a farmer comes in and finds two or three dead broilers, his margins are so tight, he just doses all of them, period. No question about it.

Mr. VOLKMER. He—he gives a large dose to them.

Dr. KASS. Absolutely, therapeutic doses right down the line.

Mr. VOLKMER. Because if he doesn't, he runs the risk of losing that whole flock, doesn't he?

Dr. KASS. It has happened. They'll come in the next day and the whole flock's dead.

Mr. VOLKMER. Yeah.

Mr. GORE. Well, I want to thank the members of this panel and the witnesses throughout today and yesterday. We've tried to have a very balanced and fair hearing to look at this question of antibiotic resistance from all sides. I think that the—the evidence clearly indicates that some actions are needed. We will continue—I say we—the subcommittee, I'm sure, is going to continue its interest in this area and we will have some recommendations in the form of a report at a later time.

With that, the hearing is adjourned.

[Whereupon, at 1 p.m., the subcommittee was adjourned.]

APPENDIX I

MOLECULAR EPIDEMIOLOGY OF ANTIBIOTIC RESISTANCE IN SALMONELLA FROM ANIMALS AND HUMAN BEINGS IN THE UNITED STATES

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Abstract We collected serotyped isolates of salmonella from reference laboratories in the United States, tested their susceptibility to antibiotics, and extracted plasmids from isolates that were resistant to a different combination of antibiotics from each of three serotypes. Restriction-endonuclease digestion showed that within each of the three groups, plasmid molecules from animal and human isolates were often identical or nearly identical.

One serotype–plasmid combination appeared to be endemic in cattle in 20 states and infected 26 persons in two states. The human cases, which were not recognizably related except for their common plasmids, appeared to be clustered in time but geographically dispersed, like cases in previous outbreaks spread by food products. These findings suggest that resistance plasmids may be extensively shared between animal and human bacteria, and that spread of multiresistant strains of salmonella among animals and human beings, as observed in Britain, may have been undetected in the United States for lack of comparable surveillance. (N Engl J Med. 1982; 307:1-6.)

NEARLY half the antibiotics sold in the United States are given to animals, most of which are eaten by people.[1] Antibiotics are given to animals to treat and prevent disease, and low concentrations are given to promote growth. One of the persisting controversies about these practices is whether bacteria made resistant to antibiotics by exposure to them in animals spread to human beings.[2] Spread to farm workers has been demonstrated.[3,4] It has proved difficult, however, to determine whether any strain of resistant bacteria isolated from a person has come from an animal.[5]

A newly available approach takes advantage of the fact that bacterial antibiotic-resistance genes are commonly carried on plasmids, which are independently replicating genetic elements separate from the bacterial chromosome and often transferable between bacteria.[6] Plasmids are large enough and subject to enough evolutionary events to generate discriminating structural variation.[7] They are also small enough to be extracted from bacteria separately from their chromosomes and analyzed with newer techniques for characterizing or "fingerprinting" DNA molecules.[8] We used one of these methods — restriction-endonuclease digestion — in studies of antibiotic-resistance plasmids in animal and human isolates of salmonella, a pathogen in both.

From the Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, the Departments of Microbiology and Molecular Genetics, Harvard Medical School, and the Massachusetts Public Health Department, Boston; the Department of Medicine of the Miriam Hospital and Brown University, Providence, R.I.; the National Veterinary Services Laboratory, Ames, Iowa; the State of Wisconsin Department of Health and Social Services, Madison, Wis.; the Microbial Disease Laboratory of the California State Department of Health, Berkeley, Calif.; and the Department of Veterinary Microbiology School of Veterinary Medicine, Purdue University, Lafayette, Ind. Address reprint requests to Dr. O'Brien at the Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

Supported under contracts (223-78-3015 and 223-79-7060) with the Food and Drug Administration and in part by a grant (GM 28142-01) from the National Institutes of Health.

METHODS

Consecutive isolates of salmonella submitted to reference laboratories were collected and forwarded after serotyping to one laboratory (at Brigham and Women's Hospital) for antibiotic-susceptibility testing and plasmid studies. The isolates were collected over 2½ years from the Massachusetts State Laboratory, over two years from the National Veterinary Services Laboratory, and over three to six months from six other state laboratories.

Antibiotic-susceptibility testing was performed with a standard disk-diffusion method using commercially prepared disks (BBL Laboratories) and 150-mm Mueller–Hinton plates (Gibco Diagnostics). Zone diameters were recorded in millimeters and computer filed for analysis as described previously.[9] Minimal inhibitory concentrations of tetracycline were determined in dextrose phosphate broth.

β-Lactamases were identified by isoelectric focusing in polyacrylamide gel developed with a chromagenic cephalosporin.[10]

Plasmid DNA was prepared from 6-ml overnight cultures, according to a modification of the procedure of Birnboim and Doly.[11] Restriction-enzyme digestion was performed for 2½ hours at 37°C with the buffers recommended by the manufacturer (New England Biolabs). DNA fragments were fractionated electrophoretically through 0.7 per cent agarose gels in buffer containing TRIS and acetate.[12] DNA for transformation was purified by equilibrium centrifugation in cesium chloride density gradients containing ethidium bromide. Plasmids were transferred in mating experiments to the *Escherichia coli* K-12 SY663 *trp*$^{\nabla}$ *met*$^{-}$ *his*$^{-}$ *nal*^{r} *rif*^{r} *hsdR*. Transformation of this DNA into competent *Esch. coli* K-12 cells was performed according to the techniques of Cohen et al.[13]

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When plasmids were compared, the observed sizes of all plasmid fragments present after restriction-endonuclease digestion were treated as binary variables, and each of these variables was scored as present or absent for each isolate. A standard computer subroutine for cluster analysis (BMD P2M,[14] which used a Euclidean distance metric and an average linkage algorithm) arranged the plasmids according to their degrees of similarity in the presence or absence of the variables.

Results

Salmonella typhimurium var. *copenhagen*

A 2½-year survey of β-lactamases in human isolates of salmonella in Massachusetts revealed 17 cases of infection with *Salmonella typhimurium* var. *copenhagen* containing the rare OXA-2 β-lactamase (Fig. 1).[10] Thirteen of the cases occurred within two two-month periods. None of the isolates from these cases had any zones of inhibition around the susceptibility-test disks for ampicillin, streptomycin, kanamycin, or sulfonamide, indicating resistance to high concentrations of these agents. All had small zones of inhibition (8 to 14 mm in diameter) around the tetracycline disk, indicating resistance to moderate concentrations of this antibiotic (32 μg per milliliter), instead of the more commonly observed high concentrations (250 μg per milliliter).

Fifty-one per cent of 287 animal isolates of *S. typhimurium* var. *copenhagen* — but only 6 per cent of 4350 animal isolates of other salmonella serotypes — were resistant to this same combination of antibiotics. When 32 animal isolates of *S. typhimurium* var. *copenhagen* resistant to this combination were tested, 19 (59 per cent) had the OXA-2 β-lactamase and also had small zones of inhibition around the tetracycline disk. The other 13 isolates (41 per cent) had the more common TEM-1 β-lactamase, and none of them had any zone of inhibition around the tetracycline disk. It was also noted as a practical guide to further detection of these two types that the diameters of the zones of inhibition around the piperacillin test disk were larger than those around the cephalothin disk for each of the 19 isolates with the OXA-2 β-lactamase but were smaller for each of the 13 with the TEM-1 β-lactamase.

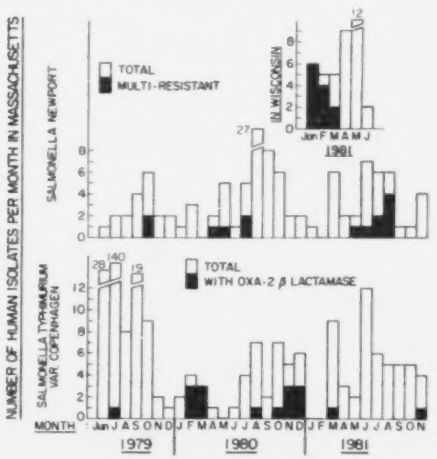
NUMBER OF HUMAN ISOLATES PER MONTH IN MASSACHUSETTS
SALMONELLA NEWPORT
TOTAL
MULTI-RESISTANT
IN WISCONSIN
Jan F M A M J
1981
SALMONELLA TYPHIMURIUM VAR COPENHAGEN
TOTAL
WITH OXA-2 β LACTAMASE
MONTH
Jan J A S O N D J F M A M J J A S O N D J F M A M J J A S O N
1979
1980
1981

Figure 1. Human Isolates of *S. typhimurium* var. *copenhagen* and of *S. newport* Submitted for Serotyping.

Isolates were collected in Massachusetts over a 30-month period and in Wisconsin over a six-month period.

The observation that multiple isolates of one salmonella serotype from animals and human beings had the same two rare resistance genes, as well as three other more common ones, suggested that they might be carrying the same plasmid or plasmids. Electrophoresis in 0.4 per cent agarose gel of undigested plasmid preparations from 12 of the isolates of *S. typhimurium* var. *copenhagen* with the OXA-2 β-lactamase showed that each isolate had a denser, apparently multicopy 2.4-kb (kilobase) plasmid, a 9.2-kb plasmid, and a large plasmid in the range of 90 to 110 kb. Susceptibility testing of *Esch. coli* K-12 transformants of each showed that the 2.4-kb plasmid carried genes for resistance to streptomycin and sulfonamides, and that the 90-kb to 110-kb plasmid had genes for resistance to streptomycin, kanamycin, and ampicillin and to moderate levels of tetracycline.

When similar plasmid preparations of animal and human isolates of *S. typhimurium* var. *copenhagen* with the OXA-2 β-lactamase were digested with the EcoR1 restriction endonuclease, and the resulting DNA fragments were separated by agarose gel electrophoresis, the large plasmid was cleaved into nine or more fragments (Fig. 2 and 3). The 2.4-kb and 9.2-kb plasmids remained single bands after digestion, as shown in an isolate that lacked the 2.4-kb band (Fig. 2, lane 2) and a transformant that lacked both bands (lane 6).

Most of the DNA fragments from the large plasmid were common to most of these OXA-2-carrying isolates. Rarely, however, did all the fragments of the large plasmid from one isolate match all those of the large plasmid from another. Exceptions were the plasmids of the isolates (Fig. 3, lanes 13 through 18) from five of the six persons infected in Massachusetts in February and March of 1980, all of which had identical fragments. Several other pairs of isolates from one species and one state also had identical fragments. Otherwise, as emphasized in Figure 3, plasmid DNA fragments of OXA-2 carrying *S. typhimurium* var. *copenhagen* isolated from some persons often matched those from animals more closely than those from other persons.

DNA fragments of plasmids from three isolates of *S. typhimurium* var. *copenhagen* with the TEM-1 β-lactamase (Fig. 3, lanes 52 through 54) appeared to be unrelated to those from any of the 51 isolates of the same serotype with the OXA-2 β-lactamase. Those from the single human isolate of *S. typhimurium* var. *copenhagen* with the TEM-1 β-lactamase appeared to be largely unrelated to those from the two bovine strains isolated in Nebraska and Missouri, which were closely related.

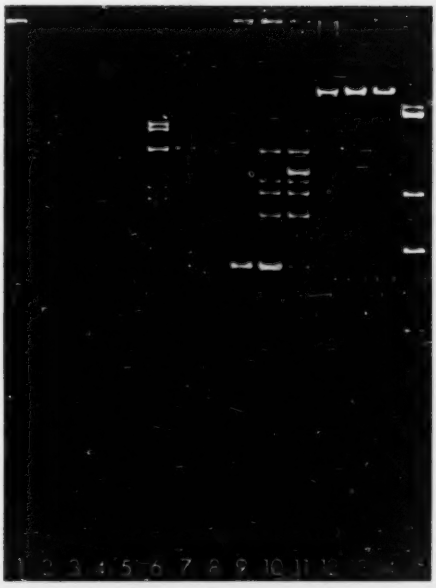

Figure 2. Agarose Gel Electrophoresis of DNA Fragments from *Eco*R1 Digests of Plasmids Extracted from Isolates of Salmonella.

The fragments in lanes 1 through 8 are from OXA-2-carrying isolates of *S. typhimurium* var. *copenhagen*. Those in lanes 1, 2, and 3 are from bovine isolates from Idaho, Utah, and North Dakota, respectively. Those in lanes 4 and 5 are from human isolates from Massachusetts. Lane 6 shows a transformant of the isolate in lane 5. Lane 7 shows a bovine isolate from Missouri, and lane 8 a human isolate from Massachusetts.

The fragments in lanes 9 through 11 are of plasmids from isolates of *S. newport*. Lane 9 shows a porcine isolate from Nebraska, and lanes 10 and 11 show human isolates from Wisconsin and Massachusetts.

The fragments in lanes 12 through 14 are of plasmids extracted from transconjugants of isolates of *S. dublin*. The plasmid in lane 12 is from a bovine isolate, and that in lane 13 from a human isolate, both from California. Lane 14 shows a bovine isolate from Indiana.

Lane 15 shows λ phage fragments as size standards. The lower of the pair of bands at the top is 23.9 kb, and those below are (in descending order) 9.5, 6.7, 4.4, 2.3, and 2.0 kb.

A majority (106 of 160) of the animal isolates of *S. typhimurium* var. *copenhagen* with the OXA-2 β-lactamase were bovine. These bovine isolates came from 20 states that were mostly in the West and Midwest, and represented 13 per cent of the 827 isolates of bovine salmonella sent from those states to the reference laboratory during the two-year observation period.

The 17 persons infected with OXA-2-carrying *S. typhimurium* var. *copenhagen* in Massachusetts lived in different parts of the state, and epidemiologists found a possible connection only between two, who had been hospitalized at the same center. These two were among five patients studied in February and March 1980 whose isolates had identical *Eco*R1 plasmid fragments. Another patient from this group, who was receiving steroid therapy for colitis, had a relapse eight months later; an isolate obtained at that time yielded the same *Eco*R1 plasmid fragments (Fig. 3, lanes 13 through 18). Two other patients whose isolates (obtained a week apart) had identical *Eco*R1 plasmid fragments (Fig. 3, lanes 31 and 32) lived in adjacent communities. The nine persons in California noted to be infected with OXA-2-carrying *S. typhimurium* var. *copenhagen* during the four-month survey of reference isolates (Fig. 3, lanes 27, 36, and 50) lived in different parts of the state.

Salmonella newport

When human salmonella isolates serotyped by the Wisconsin State Laboratory of Hygiene during the first six months of 1981 and forwarded to us were tested for antibiotic susceptibility, we noted 13 isolates of *S. newport* resistant to tetracycline, streptomycin, sulfonamide, and ampicillin. Plasmid preparations of each of these 13 isolates and two similar isolates obtained earlier from pigs in Nebraska yielded identical DNA fragments after *Eco*R1 digestion (Fig. 2, lanes 9 and 10). Subsequent investigation by state epidemiologists disclosed that the 13 cases occurred in 10 households in nine different counties over a three-month period (Fig. 1), with no apparent link between the households.

Similar digests of plasmid preparations of the 14 multiresistant human isolates of *S. newport* obtained during the 2½-year Massachusetts survey (Fig. 1) showed that nine had half or more of their DNA fragments in common with the Wisconsin human isolates or the Nebraska pig isolates. The four Massachusetts isolates with the most fragments in common with the others were resistant to the same antibiotics (e.g., Fig. 2, lane 11), whereas those with fewer fragments in common either lacked resistance to sulfonamide or lacked resistance to sulfonamide and, in addition, had resistance to kanamycin. *Eco*R1 digests of plasmid preparations from three isolates resistant to the same combination of antibiotics but resistant to only moderate levels of tetracycline, or to the same combination but to chloramphenicol as well, had no fragments in common with the other digests or with each other.

Salmonella dublin

Thirty-nine per cent of 158 animal isolates of *S. dublin*, but not more than 4 per cent of those of any other serotype, were resistant to tetracycline, streptomycin, kanamycin, and ampicillin. This resistance was transferred to *Esch. coli* K-12 in mating experiments. *Eco*R1 plasmid digests of transconjugants from 10 bovine isolates of *S. dublin* from six states and from two human isolates noted in the four-month California survey were all resistant to these four antibiotics, and all had identical DNA fragments (Fig. 2, lanes 12 and 13). A transconjugant from a bovine isolate from Indiana that was resistant to these same antibiotics and also to chloramphenicol and sulfonamide had the same DNA fragments as the others, but it also had 10 addi-

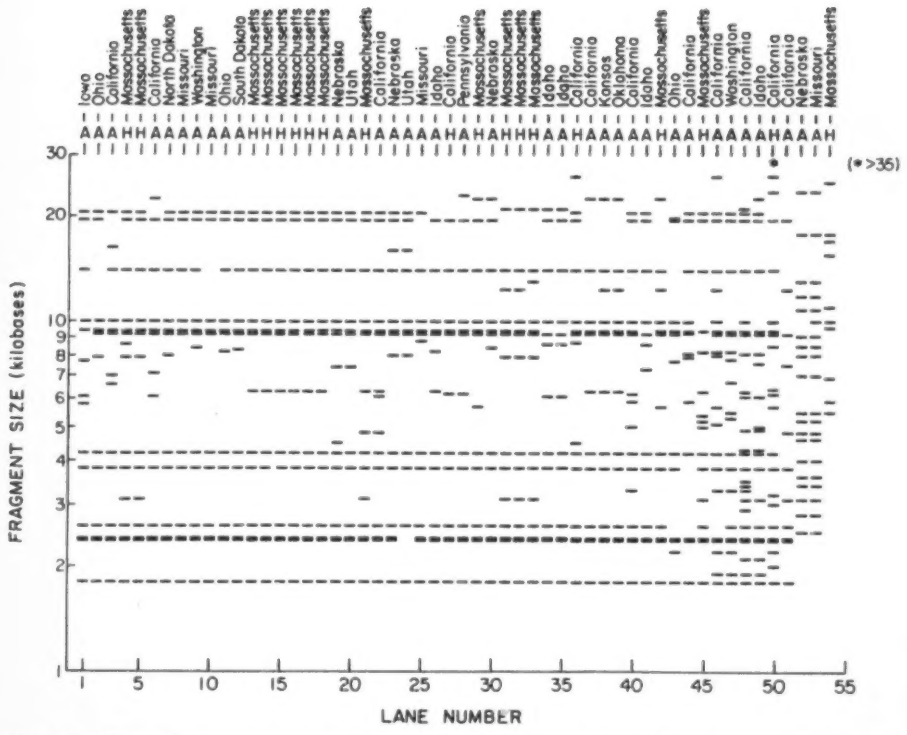

Figure 3. DNA Fragments Produced on Agarose Gel Electrophoresis of *Eco*R1 Digests of Plasmids of *S. typhimurium* var. *copenhagen*. Isolates were arranged by computer so that those with the most fragments in common were closest to each other (see Methods). The isolates in lanes 1 through 51 carried the OXA-2 β-lactamase, and those in lanes 52 through 54 TEM-1 β-lactamase. A denotes animal, and H human being.

tional fragments (Fig. 2, lane 14), suggesting the presence of an additional plasmid.

Discussion

Because a restriction endonuclease cleaves a DNA molecule only at sites that have specific nucleotide sequences, the lengths of the cleaved fragments between these sites characterize the molecule.[8] We and others have recently used this technique to demonstrate that identical antibiotic-resistance plasmids could be found in isolates of different species of bacteria from patients in the same or neighboring hospitals.[15-19] We have now used the technique to show that identical or nearly identical antibiotic-resistance plasmids may be found in salmonella isolated from animals or persons in widely separated parts of the United States.

Earlier, Anderson and Threlfall and their co-workers observed repeated outbreaks in which multiresistant salmonella of one serotype or phage type spread throughout calves in Britain or the Continent and then also infected human beings.[20-22] They observed these outbreaks because they had systematically surveyed antibiotic resistance in human and animal isolates of salmonella in Britain for many years and so could detect the onset of each new outbreak and trace its subsequent spread. Our observations are restricted to a comparatively short time, and our human isolates came from only a few states. Nonetheless, the endemic distribution of OXA-2-carrying *S. typhimurium* var. *copenhagen*, which we have determined to have nearly identical plasmid molecules, in cattle from 20 states and its isolation from 26 infected people are consistent with one phase of the type of outbreak seen in Britain.

We can infer more about the sequence of spread of the multiresistant *S. dublin* isolates. For many years infection with *S. dublin* was confined to cattle and people in California and adjacent states, but in the past

decade it has been reported progressively from more eastern states.[23] The acquisition by multiresistant *S. dublin* of an additional plasmid with resistance to chloramphenicol and sulfonamide in one of the later areas to be involved is a phenomenon repeatedly observed in Britain, usually after a shift in antibiotics used to contain the spread.[20,22]

Some observers have attributed the outbreaks observed in Britain in part to certain calf-rearing practices there.[24,25] Our results, however, indicate that similar outbreaks may have occurred in the United States and been undetected for lack of comparable surveillance. Separate state reference laboratories collect and serotype human isolates of salmonella in the United States, and a federal laboratory collects and serotypes animal isolates.[23,26] However, the antibiotic resistance of these isolates is not often tested or analyzed, and to our knowledge no search has been made to detect identical antibiotic-resistance plasmids.[27-29] Our finding of plasmids common to animal and human isolates for each of the first three antibiotic-serotype combinations that we examined, using a limited sample of human isolates, suggests that comprehensive surveillance in the United States would uncover additional examples.

These results reemphasize the unique potential of isolates of salmonella for tracing the spread of antibiotic resistance through large and dispersed populations of animals and human beings. In the flora of both, salmonella are sparsely distributed and made conspicuous by the disease that they produce, and they can be selectively isolated, centrally collected, and elaborately serotyped; all these factors facilitate finding the same strain in widely separated hosts.[26] Yet, although suited as tracers of the spread of resistance, isolates of salmonella may greatly underrepresent its magnitude. Among human beings each culture-documented case of infection due to salmonella has been estimated to represent as many as 100 undocumented cases.[30] Moreover, other, far more prevalent Enterobacteriaceae such as *Esch. coli*, may acquire resistance plasmids as readily, and spread in much larger numbers through the same routes, as the rare but traceable salmonella.[31]

To improve our chances of finding the same resistance plasmid in animals and persons in different parts of the United States, therefore, we examined only isolates with certain antibiotypes belonging to particular serotypes of salmonella. Accordingly, the spread of each plasmid that we observed may represent spread of one or a few strains carrying it; its transfer to other serotypes or genera has not yet been sought.

We found that one antibiotype in one serotype — i.e., resistance to tetracycline, streptomycin, kanamycin, sulfonamide, and ampicillin in *S. typhimurium* var. *copenhagen* — was produced by at least two apparently unrelated plasmids. The majority of the isolates from animals had moderate levels of resistance to tetracycline and the OXA-2 β-lactamase, and plasmids from all of these isolates were closely related (Fig. 3). The minority of isolates carrying TEM-1, however, were still more prevalent than the isolates of this antibiotype in any other serotype, suggesting that resistance to this combination of antibiotics may be particularly advantageous for the ecologic niche of *S. typhimurium* var. *copenhagen* and that this resistance has come to be provided by more than one plasmid. Conversely, *S. newport* isolates resistant to four antibiotics, and other isolates resistant to three of the antibiotics or to three plus a different antibiotic, had half or more of their cleaved fragments in common.

The infected patients whom we observed were not farm or meat-industry workers, which leaves home preparation and consumption of food products as their most common potential contact with the bacteria from food-source animals.[5] Consistent with this route of transmission was the clustering in time of geographically dispersed cases, such as those of the multiresistant *S. newport* in Wisconsin and of the OXA-2-carrying *S. typhimurium* var. *copenhagen* in Massachusetts. This pattern was observed previously when salmonella contaminated batches of food products, such as cheese,[30] powdered milk,[32] chocolate balls,[33] or hamburger,[34] were disseminated in many states through food-distribution systems such as grocery chains. Each batch produced culture-documented infections in only a small fraction of its widely scattered consumers, presumably because of cooking, underdetection of infected cases as mentioned above, and variations in inocula and host resistance to infection. In our study we probably observed only parts of outbreaks because we were not simultaneously monitoring human isolates in adjacent states and because the Wisconsin outbreak seemed to be under way when our observation period began.

The minor variations in structure of the plasmids from 51 isolates of *S. typhimurium* var. *copenhagen* with the OXA-2 β-lactamase shown in Figure 3 presumably represent the occurrence in nature over time of recently recognized events, such as insertion of transposons or deletion by recombination between homologous nucleotide sequences[35]; in this study these events generated an extraordinary range of epidemiologic markers. These plasmids share enough structure to indicate that they have a common origin, but they also exhibit enough diversity to make it possible to distinguish strains that would otherwise be indistinguishable. Moreover, mapping techniques to determine the order of the restriction fragments in the plasmid molecule might further refine plasmid epidemiology by permitting reconstruction of a genealogic sequence for these structural changes.

This type of plasmid epidemiology could be more fully used if more or all salmonella isolates in the United States were screened for antibiotic resistance and plasmids from selected isolates were digested and analyzed. This could probably be done with a small increase in what it now costs to isolate and serotype salmonella and investigate their epidemiology.[26] The results would provide a measure of the interchange of

antibiotic resistance between animal and human flora, which could be entered into cost-benefit analyses of antibiotic use in animals. Such studies could also detect more unrecognized outbreaks, and (particularly if not performed in retrospect, as ours was) they could increase the chances of identifying and tracing vehicles of spread in some of them. In addition, such studies would monitor spread of resistant strains in animals and perhaps suggest ways of containing it.

If the plasmids of the OXA-2-carrying *S. typhimurium* var. *copenhagen* had circulated separately in animal and human flora, their structures might be expected to have evolved divergently. Figure 3 indicates that this did not occur. When the plasmid digests are arranged so that those with the most fragments in common are closest, those from animal isolates alternate with those from human isolates.

The molecular variants shown in Figure 3 also provide an unusual glimpse of plasmid evolution.[36] The genes that come to be carried on an evolving plasmid determine not only the antibiotic resistance of its bacterial hosts but also the range of bacterial hosts to which it can spread and the stability of its persistence in them.[37] Exposure to an antibiotic amplifies the prevalence of a resistance plasmid by some factor, and so also amplifies its opportunity to evolve. After the plasmid has evolved, an identical reexposure might amplify its prevalence by a larger factor.[38] Figure 3 thus raises the possibility that the effect on human beings of antibiotic usage in animals may not be measured only by the number of resistant strains interchanged but also by their evolved potential for spread and persistence in human flora.

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SURVEILLANCE OF THE FLOW OF SALMONELLA AND CAMPYLOBACTER IN A COMMUNITY

Prepared for:

United States Department of Health and Human Services
Public Health Service
Food and Drug Administration
Bureau of Veterinary Medicine

By:

Communicable Disease Control Section
Seattle-King County Department of Public Health

Contract Number: 223-81-7041
August, 1984

City of Seattle
Charles Royer
Mayor

King County
Randy Revelle
County Executive

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The Center for Veterinary Medicine makes the following statement regarding this report:

The Seattle-King County Department of Public Health submitted the final report of contract 223-81-7041 to FDA on August 31, 1984. This project included the study of Salmonella and Campylobacter isolated from various types of meat, a poultry processing plant, human patients and controls, pets and the environments surrounding these subjects. The data also include information obtained from questionnaires administered to human patients and people who served as controls for the patients. The report contains sufficient summaries, analyses and interpretation of data and conclusions to be acceptable under terms of the contract. Acceptance of the report does not necessarily mean, and should not be construed to mean, that FDA endorses or does not endorse the findings reported by the contractor.

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I. ABSTRACT

In an effort to learn more about possible linkages between human infection with Salmonella and Campylobactor jejuni and contamination of food by those bacteria, a two-pronged surveillance system was established. Food of animal origin from retail outlets in King County was systematically cultured for Salmonella and C. jejuni for a period of 20 months. Simultaneously, cases of Salmonella and C. jejuni enteritis diagnosed in enrollees at Group Health Cooperative of Puget Sound, a 320,000 member health maintenance organization, were investigated. A case/control study was included in the evaluation of the C. jejuni infections.

Salmonella and C. jejuni isolates from food and human cases were subjected to antibiotic susceptibility testing, plasmid analysis, and serotyping in an effort to identify phenotypic characteristics which might facilitate comparisons between the two groups of isolates.

The predominant finding in the food surveillance system was contamination of retail poultry by C. jejuni; 192 (22.3%) of 862 specimens cultured C. jejuni, only 30 (3.5%) cultured Salmonella. Other types of retail meat had, at most, negligible contamination by either bacterium.

In the population under study, C. jejuni was found to be a more common enteric pathogen than Salmonella. During the period of case surveillance, 218 C. jejuni cases (matched with 526 controls) and 72 Salmonella cases were diagnosed and investi-

gated. The case/control study disclosed that a number of exposures during the 7 days prior to the onset of illness were associated with cases more frequently than with controls, thus implicating those exposures as risks for C. jejuni infection. The most prominent of those exposures were travel to undeveloped countries, drinking raw milk, consumption of chicken, exposure to untreated water, contact with humans ill with enteritis, and contact with pets, particularly dogs, with diarrhea.

Calculation of the "etiologic fraction," the proportion of all cases attributable to specific exposures, revealed that consumption of chicken was responsible for 48.2% of cases of C. jejuni enteritis in the Group Health population during the period of study.

The information provided by the case/control study showing that chicken consumption was the predominant risk factor associated with C. jejuni enteritis was supported by microbiological study of C. jejuni isolates. Thus, isolates from human cases and those from retail poultry had similar antibiotic susceptibility patterns including prevalences of 29.7% and 32.8%, respectively, of tetracycline resistance, which was found to be plasmid-mediated. In addition, the distribution of the six most frequent Lior serotypes of isolates of C. jejuni from retail poultry was identical to that among isolates from humans.

In summary, work performed under Contract #223-81-7041 indicates that enteritis due to Campylobacter jejuni is more common than that due to Salmonella. Furthermore, C. jejuni does appear to flow from chickens to man via consumption of poultry products.

II. INTRODUCTION

Man's foods have long been known to be a source of human disease. Foremost among the types of illneses that man acquires from food are infectious diseases, among the most prominent of which, from a historical perspective, are tuberculosis, typhoid fever, viral hepatitis, brucellosis, botulism, trichinosis, paragonimiasis and salmonellosis. As the epidemiology and pathogenesis of the most serious of the infections of man associated with food have been delineated, specific methods for their prevention have become apparent. For example, foodborne tuberculosis is prevented by simple pasturization of milk; botulism, by adequate sterilization of preserved foods; typhoid fever, by abstinence from food preparation by chronic enteric typhoid carriers.

Even though the most dramatic of the foodborne human infections have been brought under control in developed countries, the problem has not disappeared. Interest in foodborne infections is currently focused on diseases such as salmonellosis, a diarrheal infection of low mortality but great incidence, perhaps as many as 2 million episodes per year in the United States alone (1). Salmonella organisms are widely distributed throughout the animal kingdom as

pathogens in some circumstances and as part of the normal intestinal flora of many species.

It is certain that a proportion of human salmonellosis is acquired from food of animal origin; this fact is best exemplified in foodborne outbreaks in which the infecting strain, identified usually by serotyping, is also isolated from food that ill individuals consumed.

Nevertheless, documented foodborne salmonellosis represents only a small proportion of all cases in countries such as the U.S. and England where national surveillance is maintained. In the U.S. in 1979, the last year for which data are available, 67 foodborne outbreaks involving 4,053 persons were reported to the Centers for Disease Control, but these cases represented only 13 percent of the 31,123 total Salmonella reports (2).

Even though foodborne outbreaks represent only a small proportion of all Samonella cases, there is reason to believe that many sporadic cases of salmonellosis are acquired from food. For example, among the six most frequent serotypes of Salmonella infecting humans in the U.S. in 1979, four (S. typhimurium, S. agona, S. infantis, S. heidelberg) were among the six most prevalent serotypes isolated from animals and animal-derived food that year (2). Information such as this has persuaded the public health establishment in England that salmonellosis is a widely prevalent infection introduced into humans by contaminated

animal flesh, milk, and eggs (3).

Despite the widely-held attitude that human salmonellosis is a zoonosis and that animals are the immediate reservoir of most Salmonella infections in humans, it has been difficult to document this fact with solid epidemiological evidence. Investigators at the U.S. Centers for Disease Control have recently concluded that the vast majority of human Salmonella infections have an unknown source (4). This doubt has led to the rejection, in the U.S. at least, of initiatives for a national program for Salmonella control in processed foods (5).

An important ancillary issue has been raised during the debate about the epidemiology of human Salmonella infections. In recent years there has been an increase in antibiotic resistance among bacteria pathogenic for humans. Infections caused by bacteria that have gained such resistance are often more difficult to cure because choices of antibiotics for therapy may be limited.

The recent emergence of antibiotic resistant pathogenic bacteria in human infections correlates with, and is without doubt related to, the increasing usage of antimicrobial drugs in human medicine during the past 40 years. However, another pathway for acquisition of antibiotic-resistant bacteria by humans is contaminated food derived from animals that have been given antibiotic-supplemented feed. Feed supplementation with subtherapeutic doses of antibiotics is

common in commercial animal husbandry and is known to produce antibiotic-resistant bacteria in animals' resident enteric flora (6,7). Furthermore, spread to humans of antibiotic-resistant Salmonella via contaminated meat is well-documented (8,9).

Thus, the possible relationship linking first, antibiotic supplementation of animal feed; secondly, antibiotic resistance among bacteria in food-producing animals; and thirdly, infection due to antibiotic-resistant bacteria in humans, is a prominent issue underlying the efforts to quantify the extent of human salmonellosis that is attributable to animal sources. To the extent that those efforts have not been successful (5), the associated issue of transfer of antimicrobial resistance from animal to man via food also remains open.

Against this background of frustration in assigning a magnitude to the problem of human illness attributable to Salmonella contamination of food derived from animals, another potentially important foodborne bacterial pathogen has recently emerged. Campylobacter jejuni has in recent years been identified as a human enteric pathogen as prevalent or more so than Salmonella and Shigella (10,11).

Like Salmonella, Campylobacter jejuni is widely distributed in the animal kingdom as an intestinal commensal and, perhaps, a pathogen. Most commercially-raised poultry have C. jejuni in their intestinal flora (12,13). Cattle, swine,

and sheep may also harbor this bacterium.

Recent studies show that foods produced from these animals may also be contaminated by C. jejuni. Thus, the organism has been isolated from chicken carcasses in retail markets (14) and, to a lesser extent, from beef and pork (15,16). The route of contamination in each instance is considered to be intestinal spillage during processing.

The epidemiology of human C. jejuni infections is still being delineated. Several types of transmission to and among humans have been documented or implicated: direct contact with pet animals (17); drinking unpasteurized milk (18,19); foodborne and waterborne outbreaks (20,21); and person-to-person, including perinatal, transmission (22,23). However, like salmonellosis, C. jejuni enteritis usually occurs in sporadic fashion, without an obvious origin.

Because of the extent of contamination of live and processed poultry with C. jejuni, it has been tempting to speculate that a significant proportion of human C. jejuni infections are acquired from that source, either during preparation or ingestion of contaminated poultry. Indeed, two recent pilot studies have now implicated chicken eating or chicken preparation as a risk factor for sporadic C. jejuni enteritis (24,25).

Thus, in view of the frustration in proving that the sporadic case of salmonellosis is acquired from animal-derived food, the emerging results suggesting that many C.

jejuni infections are acquired from food have encouraged those who are interested in assessing the magnitude of the problem of human acquisition of infection, and more specifically, antibiotic-resistant infection, from animal-derived foods.

Among those interested in this issue is the U.S. Congress. In 1978 Congress provided to the Food and Drug Administration an appropriation to evaluate epidemiological approaches to the effects on human health of the subtherapeutic use of antimicrobials in animal feed. The expert committee that was convened to conduct this evaluation concluded that "postulations concerning the hazard to human health that might result from the addition of subtherapeutic antimicrobials to feeds have been neither proven or disproven (26)." The research necessary to establish and measure a definite risk, in the Committee's opinion, could not be an all-encompassing study. Rather, the committee suggested that future studies be epidemiological in scope, and carefully designed to fill gaps in present knowledge. The committee's assessment of current research needs included surveillance of antimicrobial resistance of bacteria in animals, in meat and meat products, and in humans, and studies on the epidemiology of plasmid-mediated resistance to antimicrobials in animals and humans (26).

From the points raised in this introduction it can be appreciated that the issues raised by human foodborne infec-

tion continue to warrant careful scientific scrutiny. Many old problems in this area have been solved, but important ones such as the magnitude of foodborne salmonellosis and C. jejuni, and the human health implications of antibiotic-supplementation of animal feed, persist and must continue to be addressed.

III. OBJECTIVES

The primary purpose of this project, as stated in Contract #223-81-7041 between the Food and Drug Administration (FDA) and Seattle-King County Health Department (SKCHD), was to study the relationship between the occurrence of Salmonella spp. and Campylobacter jejuni in foods of animal origin and the occurrence of human illness caused by those two organisms. Thus, for purposes of this project, Salmonella and C. jejuni were chosen to serve as models to estimate the flow of potentially pathogenic bacteria from animals to man through the food chain. The rationale for selecting these two bacteria for this study is that both are found in animals, in food, and in humans as pathogens. Within this context, there were four specific study objectives enumerated in the contract:

A. To define the character of the movement of bacteria from animal to man, using as markers Salmonella and C. jejuni in foods from animals.

B. To determine the proportion of human salmonellosis and C. jejuni enteritis which has its origin from animal foods obtained from poultry, swine, and beef.

C. To determine the magnitude and character of the problem of human illness caused by Salmonella and C. jejuni

in a defined population.

D. To utilize specific microbiological features to link human illness caused by Salmonella and C. jejuni to specific animal sources.

IV. METHODS

A. General Research Plan

The framework of the experimental design for this project were specified in the request-for-proposal (RFP #223-81-4071) issued by FDA in February 1981. This section describes the approach SKCHD chose to accomplish the work necessary to meet the contract objectives specified in the RFP and enumerated in the preceding section.

To accomplish those objectives SKCHD, the prime contractor, chose a multidisciplinary approach using epidemiological, microbiological, and laboratory methods. We chose to focus our activities on *Campylobacter jejuni* because of the existence of a pre-existing surveillance system established by SKCHD in 1980 that suggested an incidence rate for *C. jejuni* of over three times that of *Salmonella spp.* infections in residents of King County, Washington.

Two surveillance systems were established, a human case surveillance system and a food surveillance system. Human case surveillance was designated to provide over 200 cases of *C. jejuni* infections during an 18-month period within the defined patient population of Group Health Cooperative of Puget Sound (GHC), a 300,000 member health maintenance organization. The unique advan-

tages of case surveillance at GHC included the opportunity to establish true disease incidence rates, and the ability to perform a population-based case/control study of C. jejuni infections. The availability of a defined population as a substrate for the case/control study permitted the derivation of "etiologic fractions" of C. jejuni infections, which are proportions of cases in the population under study that are attributable to specific risk factors.

Also incorporated into the human case surveillance design was a protocol to obtain specimens for culture from the household environments of cases that were investigated. Thus, family members of index cases, household pets, and in some cases, foods were sampled in an effort to identify reservoirs of C. jejuni in environments of reported cases.

The food surveillance system was integrated into SKCHD's existing meat inspection program and, thus, had access to all retail purveyors of meat products in King County, Washington. Added to the retail meat surveillance system was a specification for culturing poultry products at a large independent poultry processor in Seattle. This food surveillance system was designed to provide for the culture of 2,000 specimens of food products of animal origin during a 20 month period of surveillance.

C. jejuni isolates from the two established surveillance systems were subjected to several laboratory procedures in an effort to identify markers that would facilitate a study of relationships among individual C. jejuni isolates. First, all isolates were tested for susceptibility to a group of 6 antimicrobial drugs, in order to document levels of drug resistance. Secondly, several types of plasmid analyses were performed in an effort to establish homology among bacterial isolates and to identify mechanisms of antibiotic resistance. Lastly, a provision was made independently by FDA to have C. jejuni isolates from this project serotyped at the Centers for Disease Control, Atlanta, GA.

In summary, the general research plan adopted by SKCHD to fulfill the project objectives was a multidisciplinary approach utilizing epidemiological, microbiological, and biochemical information. A wide and diverse body of experimental data was generated, which provided the basis for this report.

As noted above, the SKCHD research plan focused on C. jejuni and de-emphasized Salmonella surveillance. This decision was based on a prediction of a larger number of cases of C. jejuni in the GHC population and the belief that the project objectives could best be met by a focused study on that pathogen.

Surveillance of Salmonella was also conducted and

laboratory testing of isolates derived from surveillance was performed, but both were more limited than that for C. jejuni. This fact is reflected throughout this report.

B. Food Surveillance

1. General Plan. The Food Surveillance Program was designed to provide approximately 100 culture specimens per month from retail specimens of poultry, beef, pork, and lamb. During 12 of the 20 months of food surveillance, 25 of the 100 cultures per month were taken at a poultry processor in Seattle. Each specimen was cultured specifically for Campylobacter jejuni, Salmonella species, Yersinia species, and other pathogenic enteric bacteria.

Sampling of retail meat products was integrated into the MEAT, POULTRY, RABBIT, AND AQUATIC FOOD AND INSPECTION PROGRAM conducted on an ongoing basis by SKCHD. Under this program, every retail outlet in King County holding a food permit issued by SKCHD is visited from two to twelve times per year by a Food Inspector. The purpose of the inspection, which is required by City of Seattle and King County Ordinances, is to insure the sanitation, proper labeling, purity, origin, and correct advertising of meat products.

The Food Inspection Program is conducted by four inspectors, full time Health Department sanitarians who

work under the supervision of a public health veterinarian. Each inspector operates in a given geographical area of the county, where his responsibilty is to make the required number of inspections of each licensed outlet for meat products. In order to participate in this project's Food Surveillance Program, these four Meat Inspectors were trained to collect the required specimens for culture during the performance of their routine duties.

A poultry processor was determined to be an attractive site for sampling because of the knowledge that poultry carcasses at such processors are frequently contaminated with C jejuni and Salmonella. In addition, it was known that a single processor in Seattle provided poultry to many retail outlets in King County. Thus, some comparative information was potentially available on rates and type of contamination of specimens entering and leaving the processor, as well as that of products from that processor sampled in retail outlets.

This processor's management was thus approached and acquainted with the aims of the project. Consent was given for specimens to be taken on a regular basis. This company processes 20,000 birds per day, primarily chickens. Its products are derived exclusively from poultry grown in Western Washington.

Food surveillance was conducted in two phases.

During phase I, beginning February 1, 1982, and continuing for one year, 75 samples per week were collected at retail outlets, and 25 per week were collected at the poultry processor. To accomplish this scheme, three of the Health Department Food Inspectors collected six specimens each week at a different retail outlet; the fourth visited the poultry processor one day a week and collected six specimens.

Phase II of Food Surveillance began February 1, 1983, and continued through September 30, 1983. During that eight month period, the sampling scheme was modified so that all 100 specimens per month were collected from poultry products at retail outlets. This modified surveillance scheme was selected because review of data from Phase I indicated that among retail meat products poultry was by far the most prominent one to show contamination with either C. jejuni or Salmonella. Thus, since the primary intent of the contract was to seek evidence of the flow of enteric bacteria from animal food to man, it seemed appropriate to focus on the major type of food where contamination had been detected, which was chicken, and to sample at the site in the food-handling chain closest to the consumer, the retail outlet. This modification of the original design was approved by the FDA Project Officer.

2. Food Sampling Scheme and Culture Techniques. During Phase I, the food inspectors involved in sampling retail products each week selected at random one of the outlets in their district. The six specimens for culture were all collected at that single outlet during the course of the routine inspection visit, on Monday, Tuesday, or Wednesday. Specimens from the four specified meat types, beef, pork, lamb, and poultry, were systematically collected, as well as those from cutting surfaces and saw blades to check for environmental contamination.

Each product selected for culture was opened if sealed and swabbed along its entire surface and body cavity for approximately 30 seconds using three sterile pre-packaged dacron swabs. Any juices associated with the product were collected on the swab. The swabs were then dropped into a culture tube containing 4 ml. Cary-Blair transport medium. The tube was then placed in a container providing temperatures of approximately 4 degrees centigrade by means of a frozen gel inserted into the top of the container (freezer pak model 1806, Gott Corporation, Winnfield, Kansas). Specimens were refrigerated in this manner until delivery to the SKCHD Microbiology Laboratory, usually within four hours of having been collected. When it was necessary to hold specimens overnight prior to delivery to the laboratory,

they were placed in a refrigarator.

At the poultry processor, samples were taken at six sites in the process that began with entry of live birds and ended with departure of processed birds. Always included in the weekly sampling scheme at the processor was a cloacal swab from an individual bird prior to the point where cross-contamination of carcasses began to occur. Similarly, always included was a culture of an individual bagged poultry product ready for delivery to a retail outlet.

The method of specimen collection used at the processor was similar to that described at retail outlets: swab of the selected product for 30 seconds with sterile dacron swabs; placement of the swabs in Cary-Blair transport medium; refrigeration in a portable freeze-pak; and delivery to the SKCHD laboratory, usually within four hours.

C. Human Case Surveillance

C. jejuni and Salmonella cases were derived from the population of residents of Western Washington served by Group Health Cooperative of Puget Sound (GHC). During the time of data collection the GHC patient population was approximmtely 300,000.

Cases were diagnosed by the isolation of the pathogens from stool specimens obtained by GHC practitioners and processed by the GHC Centralized Microbiology Labor-

atory.

At the time C. jejuni or Salmonella was identified presumptively in a patient's culture, the SKCHD project office was informed, and the investigation protocol described in Methods Section D, Case/Control Study, was initiated.

There is no pre-established protocol for performing stool cultures on patients seen by GHC medical practitioners. Stool specimens are collected for culture according to the judgement of individual practitioners. The guiding principal for obtaining a stool culture is an encounter with a patient with a possible enteric bacterial infection. Using this criterion, Group Health Cooperative practitioners submit 300-450 stool specimens for bacterial culture each month.

Patients for whom stool cultures are ordered generally collect specimens themselves and bring them to the laboratory associated with the clinic where they were examined. Stool specimens are set up in primary isolation cultures at that site. Unless specific instructions are given, each specimen is cultured routinely for Salmonella, Shigella, and C. jejuni. Cultures are established in four types of agar, Hectone Enteric, Salmonella-Shigella, Campy-Brucella Agar Base, and McConkey's. In addition, each specimen is inoculated into selenite broth.

Inoculated media are transported on the day of collection, generally within four to six hours of pri-

mary plating, to the Group Health Cooperative Centralized Microbiology Laboratory, where all further handling occurs. The process for isolating C. jejuni is as follows. The Campy-Brucella Agar Base plate is incubated at 42 degrees centigrade in a candle jar and is checked for growth at 48 and 72 hours. Oxidase positive colonies are subcultured at 42 and 25 degrees C. and tested for susceptibility to nalidixic acid and cephalothin. If the isolate grows at 42 degrees C. but not at 25 degrees C. and is resistant to cephalothin but susceptible to nalidixic acid, it is given presumptive identification as C. jejuni. Isolates given that presumptive identification were inoculated into Campy-Thioglycolate broth and transported to Seattle-King County Health Department Microbiology Laboratory for confirmation and further processing.

Cultures for Salmonella received a standard evaluation. Isolates that did not ferment lactose on primary plating agar were subcultured on triple sugar iron agar, Lysine-Iron Agar, and tested for Urease production. Subcultures showing typical results (TSI: alkaline butt, acid slant, gas +/- H_2S; Lysine-Iron Agar: alkaline butt, alkaline slant; urease negative) are further tested with a packaged micro-method system for enteric organisms produced by Analytab Products, Inc. If positive for Salmonella on API Testing, the isolate is

reacted with Salmonella serogrouping antiserums, reported and transferred to Seattle-King County Health Department Microbiology Laboratory for confirmation and further handling.

D. Case/Control Study

1. Subject Selection

Case Selection. We identified all GHC Enrollees with C. jejuni infection living in King and Southwest Snohomish Counties (as evidenced by the zip code of their residence), cultured in the GHC Centralized Microbiology Laboratory. Those without telephones, who had moved out of the study area, or who did not speak English were eliminated. The remaining cases were then eligible for inclusion in the study. Only the index case (the first case identified in each household) was interviewed unless: 1) a second case was reported in the household at least two months after the first identified case, or 2) a second case was found to be infected with a different strain.

The patient's physician was contacted by an interviewer assigned to the case as soon as a positive stool culture was identified. (The process for stool collection and culture handling at GHC is described in Methods Section III.C. Human Case Surveillance). The interviewer contacted the patient after confirming that: 1) patient was informed of the diagnosis by the physician, and 2) the physician's office granted permission to contact the patient.

Patients were then contacted by phone and invited to participate in the study (form #1, Appendix A). If the patient agreed, an interview date was chosen, and the patient was visited in his/her home.

During the interview, the patients were presented with a consent form (form #2, Appendix A) and were queried (form #3, Appendix A) about their illness, animal and human contacts, foods eaten, water exposures, and household members as well as demographic information. Stool samples and/or rectal swabs were either collected immediately from all household members and their animal contacts or requested for later submission for processing at SKCHD Microbiology Laboratory. Written instructions (form #4, Appendix A) were left regarding sample collection and sample pick-up locations through an existing SKCHD transport system throughout the study area. If samples were not received within two days, follow-up phone calls and occasionally repeat visits were performed. All patients were also asked about the duration of their illness, health status of family members, and medications during follow-up phone calls.

Stools or rectal swabs were kept refrigerated until they were transported, and if more than a one-day delay in specimen transport was anticipated, interviewers were instructed to pick up the samples themselves. Rectal swabs were transported in Cary-Blair medium.

Control Selection. The eligibility criteria for control

subjects was identical to that for cases. Only the first member of a household selected to participate was eligible for inclusion in the study. Controls were first selected systematically by computer from the GHC Enrollee file using zip code in order to define the study area (zip code was the only residential variable available in the file). From the computer-generated lists of potential eligible subjects, age groups were delineated and controls were chosen randomly within nine age strata (under one year, 1-4, 5-10, 11-19, 20-29, 30-39, 40-49, 50-59, and over 50) four times during the 18-month period of data collection. This frequency matching of controls to the expected age distribution of cases was done to insure sufficient numbers for comparison with cases in the younger age groups. Controls were also selected one to two months in advance of the interview in order to insure adequate representation each month and a seasonal distribution comparable to that of case interviews as season of the year was expected to be a confounding factor.

The control subjects' personal physicians were mailed a letter and a request form seeking permission to invite their patients to participate in the study. Once permission was granted, eligible con-trols were then contacted by mail and asked to return post-cards indicating willingness to be contacted for interview. Those who did not respond were telephoned within two weeks of the mailed invitation by a representative of the GHC Center for Health Studies.

Those subjects selected as controls who indicated interest

in the study were then contacted by phone by the interviewer assigned to the subject and were informed about the study. A home interview was arranged using the same consent forms and questionnaire used for cases. Every third control household was asked to submit sample from their pets while every tenth control household was asked to submit samples from the human and animal inhabitants, in the same manner as the requests made of the case household.

Salmonella Case Selection. From April through December of 1982, the first 9 months of surveillance, only patients who were infected with one of four Salmonella serotypes (anatum, dublin, cholerasuis, and typhimurium) were eligible for inclusion in the study. These four serotypes were specified for follow-up because they were suspected by FDA as the most likely ones to be associated with animal sources.

Unfortunately, considerable time delays resulted from waiting for the serotyping of the Salmonella isolates in order to determine whether or not a patient was infected with an eligible serotype. In order to reduce the time lag between diagnosis and interview of the Salmonella subjects, as of January 1, 1983, all cases of salmonellosis diagnosed at GHC and living in the study region who had telephones and spoke English were eligible regardless of serotype. Only one case per household, the index case, was eligible. If a second case occurred in a household more than two months after the first case, the second was eligible only if

he or she was infected with the different serotype from that of the first household case. If the second case in a household occurred within two months of the first, the latter was ineligible regardless of serotype.

2. Validity Checks

Some of the safeguards included a chart check on every 20th subject, validation phone calls repeating several questions not known to the interviewers on every 10th subject and "blind dummy" interviews with evaluators to check interviewers for consistency and performance. As additional safeguards, regular interviewer meetings and questionnaire reviews were conducted by the Chief Epidemiologist or Field Manager.

Finally, subjects were asked about history of cigarette smoking, in order to assist in the recognition of differential reporting by cases and controls.

3. Non-Respondent Follow-Up

In May thru June of 1984, we attempted to contact a random sample of eligible GHC Enrollees who refused participation initially as control subjects. A subset of questions from the main questionnaire was asked during a telephone interview. The questions used were those that the preliminary analysis of the main case/control study demonstrated to be the strongest risk factors for C. jejuni enteritis. This follow-up of non-respondents was intended as a means of determining to what extent the level of non-response among controls would bias the results.

4. Risk to Subjects

There were no risks to the participants other than loss of time, temporary invasion of privacy, and the potential embarrassment and discomfort of being asked to and/or submitting stool samples or rectal swabs.

5. Definition of Terms Used

Index Case. The first case to come to the attention of the health officials in a household.

Index Subjects (both cases and controls). Those subjects for whom the exposure information was determined (i.e., the interview subject).

Index Household. The household in which the index subject usually lives.

Index Date. The date of interview for controls and the date of onset for cases.

Seven days before. Any time during the week before the index date.

After the Index Date. The time period referred to in the text and used to determine transmission to the human and animal contacts of the case (i.e., enteritis in the contacts occurring after the case's onset). For cases, the time between the onset of symptoms to the interview was used. For controls a comparable time period was needed.

Initially, it was thought that cases would be interviewed an average of one week after onset thus, initially, controls were queried about illness in contacts in days 8-14 before the inter-

view. As the study progressed, it became clear that cases were interviewed, on the average, two weeks after the date of onset. Thus, four months into the study, controls began being asked about illness in contacts in days 8-21 prior to interview. Overall, the time periods for which subjects were asked about contact illness after the index date were comparable for case and control subjects.

Probability Value (also referred to as statistical significance.) The probabililty value of a statistic more extreme than the observed value under the hypothesis that there is no relationship between two factors (i.e., exposure and disease). It depends upon the observed strength of the association (magnitude of the relative risk), frequency of the disease, and the number of subjects. The probability values were, for the most part, based on the chi-square statistic and Fisher's Exact Test and were determined for the relative risk estimates, tests of association, test for trend, and test for heterogeneity.

The two-tail probability values calculated from Fisher's Exact Test were utilized whenever the expected values for the "exposed cells" were small. Two-tail probability values were also determined from the T-test statistic for differences between population means.

Relative Risk. The ratio of the incidence in the exposed as compared to the incidence in the unexposed. It reveals the strength of an observed association. The relative risk was estimated in the study from the odds ratio.

The odds ratio is the odds of disease in the exposed as compared to the odds of the disease in the unexposed which is equivalent to the odds of exposure in the cases as compared to controls. When the disease is rare in the general population (as with C. jejuni) the odds ratio approximates the relaive risk.

Etiologic Fraction (lambda), also called the population attributable risk percent. The proportion of the incidence in the population attributable to an exposure. This statistic, unlike the relative risk, depends on the frequency of the exposure in the underlying population. The etiologic fraction also depends on the relative risk. This statistic is useful in determining the impact on the incidence of a suspect etiology for C. jejuni infection.

The 95% confidence interval. This pair of numbers brackets the relative risk and tells us we are 95% confident that the true relative risk for the underlying population lies within the upper and lower limits.

Potential Confounding Factor. Any factor which is associated both with the disease of interest and the exposure under study.

Effect Modification. Defined as the presence of variation of the risk estimate across subgroups of the population.

Seasons. Seasons as defined and used in these analyses were the rainy, colder winter (November thru March) and the dryer, warmer summer (April thru October). This categorization was based on daily rainfall and temperature for Seattle-Tacoma Airport, as reported by the National Oceanic and Atmospheric

Administration.

6. Analysis

Risk Factor Analysis. The point estimate of the relative risks (RR) and 95% test-based confidence intervals (95%CI) were calculated. Whenever necessary, in order to adjust for other factors, relative risk estimates and 95% confidence intervals were calculated according to the method of Mantel-Haenszel (28) and Miettinen (29), respectively. Additionally, trends in relative risks associated with two or more exposure levels were determined whenever appropriate (30). The tests for heterogeneity and trend in proportions for multilevel factors were determined as well.

Examination for Confounding. Exposures and demographic factors selected for further analysis were those associated with a relative risk of $\geq$1.5 or $\leq$0.7 in the exposed when contrasted with the risk in the unexposed which significantly differed from unity ($P \leq .10$). Further analysis for the "screened exposures" which met the above criteria involved scrutiny for significant alteration of the risk estimate associated with the exposure of interest resulting from the effect of another factor, i.e., a confounded result. All factors meeting the above criteria were considered to be potential confounding factors until adjustment for them proved otherwise.

Age and season, which were thought, a priori, to be potential confounding factors, were accommodated by the frequency matching of the distribution of the controls to the cases with

regard to both variables. Further stratification and adjustment for both factors was conducted as well to measure any residual confounding or variation in the risk estimate for the specific substrata.

The analyses of all "screened exposures" were controlled for two additional factors. Responses to these exposures were contrasted for interviews conducted before and after any refinements in the questionnaire.

Finally, the risk estimates for these exposures were examined after controlling for "interviewer" to insure bias did not explain any findings.

Etiologic Fraction. Exposures which were implicated as sources of C. jejuni infection based on the laboratory findings or the results of previous studies and which were associated with at least a 80% increase in the incidence of C. jejuni (relative risk $\geq$1.9) were selected as "causal exposures." Additionally, the increase in risk observed in those who reported such an exposure could not be explained by another factor.

The proportion of GHC C. jejuni incidence attributable to these "causal exposures," the etiologic fraction, was estimated according to the method of Walter, 1975 (31).

Effect of Modification. Examination for effect-modification resulted from contrasting relative risks among specific substrata of the data (i.e., age groups of humans).

/Strain-specific Risk Factor Analysis. Exposure information for cases infected with C. jejuni categorized as either hippurate

positive or negative and tetracycline sensitive or resistant was contrasted with the same information from the controls. The hippurate test was used as an indicator of whether or not the isolate was C. jejuni or C. coli. Tetracycline resistance was determined by the MIC method. Risk factor analysis was performed as for C. jejuni.

E. Laboratory Techniques for Isolation and Identification of C. jejuni and Salmonella Species

The SKCHD Microbiology Laboratory handled three types of specimens for isolation and identification of C. jejuni and Salmonella. [*Note: In the microbiological work associated with this study, Campylobacter jejuni and Campylobacter coli were not separated. Because the two species differ only slightly in phenotypic characteristics (10), and because C. jejuni is found more commonly in all species so far examined (10), we will refer to the two species collectively as C. jejuni]. First, the laboratory performed confirmation testing on C. jejuni and Salmonella isolates from the Group Health Cooperative laboratory. Secondly, primary isolation and identification procedures were performed on samples of food from the food surveillance network. Thirdly, similar isolation and confirmation techniques were performed on fecal and other types of specimens collected from the environment of patients with C. jejuni and Salmonella infections during investigation of cases in the human surveillance system.

The primary isolation and identification of C. jejuni in fecal specimens was performed as follows. Culture plates containing Brucella Agar Base, 5% sheep erythrocytes, and antibiotic supplementation (Campy-Bap) were inoculated and streaked with the material removed from the fecal specimen by a sterile swab. The plate was placed in an anaerobic jar, a Campy-Pak was added and activated, the jar was sealed and incubated at 42 degrees C.

After 24 hours the Campy-Bap plate was removed from the jar and examined for small, opaque, non-hemolytic colonies. Suspicious colonies were gram stained and examined for small gram-negative, slightly curved rods. If no such organisms were found the plates were reincubated for an additional 24 hours and similarly examined. If typical colonies were found at either 24 or 48 hours and gram stain showed small gram negative curved rods, then a well isolated colony from the culture plate was subcultured for purity under conditions described above. If, on the other hand, no colonies suspicious for C. jejuni were seen after 24 or 48 hours, the culture was reported as negative for C. jejuni.

Morphological and biochemical tests for the identification and confirmation of C. jejuni were performed on isolates from the plate streaked for purity. The following tests were used to confirm suspicious colonies as C. jejuni: examination for motility, growth in 1% glycine, 5% NaCl, oxidase and catalase, production of hydrogen sulfide,

nitrate, and susceptibility to naladixic acid and cephalothin.

Organisms giving reactions typical for C. jejuni were reported positive and inoculated into two tubes of Wang's media (for transport to subcontractor's laboratories for susceptibility testing and plasmid anaylsis) and into four tubes of horse serum for freezing and preservation at -70 degrees C.

Specimens for culture that were received from the food surveillance system were logged in, given appropriate identification numbers, and cultured in the following manner. The three swabs used to collect the specimen (see Methods section B,2, Food Sampling Scheme and Culture Techniques) were removed from the Cary-Blair medium and swabbed gener-ously over one-third of a Campy-Bap plate in a circular motion. The plate was then streaked for isolation, placed in a anaerobic jar with a Campy-Pak, and incubated at 42 degrees C. Following this inoculation procedure the process of isolation and identification of C. jejuni was identical to that used for the culture of fecal specimens.

Cultures received from the Group Health Cooperative laboratory for confirmation of C. jejuni were streaked on a Campy-Bap plate for purity. That plate was incubated in an anaerobic jar charged with a Campy-Pak and calalyst and incubated at 42 degrees C. Thereafter, the process of isolation and identification was identical to that described

above for fecal specimens.

In order to isolate Salmonella in fecal specimens, the specimen was inoculated into Selenite Broth, SS agar, brilliant green sulfadiazine (BGS) agar, and MacConkeys agar plates. After 24 hours of incubation at 35 degrees C., the tube containing Selenite Broth was inoculated onto SS, BGS, and MacConkeys agar and incubated again at 35 degrees C.

Examination of the agar plates at 24 hours (and also 24 hours after inoculation of the Selenite Broth) was performed for typical Salmonella colonies (non-lactose fermentors on MacConkeys and SS, fuchsia colored colonies on BGS). At least two of each type of suspicious colony were inoculated to TSI and incubated for 24 hours at 35 degrees C. Isolates giving TSI reactions characteristic for Salmonella were tested for the production of Urease and Indole. If Indole and Urease test were negative and the TSI reaction showed K/A, gas, +/- H_2S, the isolate was subcultured in MacConkeys medium for purity and then agglutinated with Salmonella antiserums, groups B, C1, C2, D, E, and polyvalent. Agglutination and biochemical tests were performed on organisms from the purified culture plates. The biochemical identification battery consisted of lactose, sucrose, salicin, adenitol, Methyl Red, Voges-Proskour, Simmon Citrate, nutrient gelatin, KCN, ONPG, indol, and Ornithine, Lysine and Arginine decarboxylase.

Isolates identified as Salmonella were then forwarded

to the State of Washington Department of Social and Health Services microbiology laboratory for serotyping by standard reference methods using Salmonella "O" and "H" antisera.

Specimens from the food surveillance system to be cultured for Salmonella were delivered to the microbiology laboratory as previously described, as swabs (3 swabs per tube) in tubes containing Cary-Blair liquid medium. Upon receipt at the laboratory the specimens were properly logged, identified, and inoculated into one tube each of Selenite (one swab) and Tetrathionate broth (2 swabs) and incubated at 35 degrees C. After 24 hours, the swab was removed from Selenite broth and inoculated to SS, BGS, and MacConkey's agar for further isolation and identification procedures as described above for fecal specimens. After 48 hours of incubation the swabs were removed from tetrathionate broth, inoculated to SS, BGS, and MacConkey's agar for further handling as described above for the isolation and identification of Salmonella.

Yersinia identification was undertaken in food culture isolates that gave A/A, gas negative reactions on TSI agar. If such isolates were motile at 25 degrees C. but non-motile at 35 degrees C, were oxidase positive, gram negative-rods, they were tested in the API system for final identification.

Isolates received in subculture from the GHC microbiology laboratory were logged, numbered, subcultured on a TSI slant and MacConkey's agar, and tested for Indole and

Urease. Then identical techniques to those described above were used to identify Salmonella species.

Pure Salmonella subcultures from all sources were forwarded on trypticase soy agar slants to subcontractors for susceptibility testing and plasmid analysis (only if the specimen also contained C. jejuni). Four tubes of inoculated horse serum were also prepared, incubated, and frozen at -70 degrees C. for future usage.

F. Methods of Antimicrobial Susceptibility Testing

1. General Methods.

Susceptibility testing of Salmonella isolates was performed by the standard disk diffusion test as recommended by the National Committee for Clinical Laboratory Standards (33). Antibiotics tested were ampicillin, chloramphenicol, erythromycin, streptomycin, tetracycline, and trimethoprim-sulfamethoxizole.

Since C. jejuni grows poorly in broth media, inocula for susceptibility tests of that organism by agar dilution, microdilution and disk diffusion were prepared from colonies that had grown overnight on Columbia agar supplemented with 5% sheep blood. Inocula for all C. jejuni susceptibility tests were standardized in 0.85% saline. All cultures and susceptibility tests were incubated in a microaerophilic atmosphere produced by Campy-Pak II gas generator envelope in a Gas-Pak jar (BBL Microbiology Systems). Inoculated plates for the three methods of susceptibility testing were

transferred to a microaerophilic atmosphere within 15 minutes after inoculation to avoid poor growth by the more oxygen-sensitive strains. The incubation temperature was 35 degrees C. for all susceptibility tests. The quality control organisms Staphylococcus aureus ATCC 25923 and Escherichia coli ATCC 25922 were included on each agar MIC plate and each time the microdilution or disk diffusion tests were run. The following antibiotics were tested: ampicillin, chloramphenicol, erythromycin, streptomycin, tetracycline, and trimethoprim/sulfamethoxazole.

2. Agar Dilution Susceptibility Testing.

The standard method for agar dilution testing as described by Washington and Sutter (34) for facultative organisms was used with the following modifications: first, the standardized inocula were prepared with colonies from overnight growth on blood agar plates; secondly, after inoculation, the agar dilution plates were incubated under microaerophilic conditions as indicated above, and the results were read after 48 hours. The endpoints were read as complete inhibition; a barely visible haze or a single colony was disregarded.

3. Broth Microdilution Susceptibility Testing.

Microdilution plates were prepared with Wilkins-Chagren broth by Micro-Media Systems, Inc. as special orders containing the six antibiotics in the same two-fold dilutions as those used in the agar dilution method. Plates were stored at -70 degrees C and used within one month of receipt. The protocol followed the package insert instructions for anaerobes except that the inoculum was prepared from an overnight culture of colonies grown on agar instead of a broth culture. A saline suspension of colonies was prepared to match the turbidity equivalent of a McFarland No. 2 standard and 0.6 ml were diluted in 13 ml of saline. The final inoculum was approximately $5x10^5$ colony-forming units per ml. Plates were placed in a Gas-Pak jar lying on its side and incubated microaerophilically at 35 degrees C for 48 hours.

4. Disk Diffusion Testing

Sterile 60 ml aliquots of Mueller-Hinton agar were melted in boiling water and poured into 150 mm agar plates. Testing was done according to recommendations of the National Committee for Clinical Laboratory Standards (27) except that the inoculum was prepared as described above to match the turbidity of a McFarland No. 3 standard. Antibiotic disks of the following potency were used: ampicillin 30 micrograms, chloramphenicol 30 micrograms, erythromycin 15 micrograms, streptomycin 10 micrograms,

tetracycline 30 micrograms, trimithoprim/sulfamethoxzaole 1.25/23.7 micrograms. Inoculated plates were incubated at 35 degrees C in large Gas-Pak jars that required three Campy-Pak II envelopes; after 24 hours the diameters of zones of inhibition of bacterial growth around antibiotic disks were measured in millimeters using calipers.

G. Methods for Plasmid Analysis

Bacterial isolates were screened for plasmid DNA by agarose gel electrophoresis of lysates of alkaline-sodium docecyl sulfate lysates as previously described (35). The pH of the lysis buffer was adjusted to 12.0. Plasmid DNA was purified through cesium chloride-ethidium bromide density gradients by ultracentrifugation (36).

Restriction analysis of the purified plasmid DNA was accomplished with site-specific restriction endonucleases (Bg Hinc II, Bc 1) purchased from New England Biolabs (Beverly, MA) and Bethesda Research Laboratories (Gaithersburg, MD) and used according to the manufacturers' directions.

DNA homology experiments were performed by transferring restriction fragments from agarose gels to nitrocellulose filters and hybridizing with characterized, radiolabeled DNA probes (37).

Conjugal matings between bacterial isolates were performed using two specified bacterial recipients. The first was E. coli HB101 (pro leu thi r-m-lac gal, Rif^r, Nal^r,

Str^r) obtained from Stanley Falkow, Stanford University, Palo Alto, Calif.; the second was a streptomycin-resistant, tetracycline-susceptible hippurate-hydrolysis negative strain isolated during the present study. Donor and recipient strains of C. jejuni were grown on Columbia blood agar plates (Prepared Media, Renton, Washington) for 18 to 20 at 42 degrees C in an anaerobic jar containing a Campy-Pak II. Organisms were harvested from the plate and suspended in tryptic soy yeast broth (Difco) to a concentration of 10^7 CFU/ml for donors and 10^8 (CFU/ml) for recipients. One-tenth milliliter of both donor and recipient cells were mixed on a Columbia blood agar plate. The plates were incubated upright for 24 h. and the organisms were washed from the plate with 1 ml of 0.85% saline.

Mating mixtures and donor and recipient controls were plated on brucella agar (Difco) containing 30 ug of streptomycin per ml or 15 ug of tetracycline per ml or both. Transconjugants were recloned three times on antibiotic-containing medium before being screened for plasmids. Matings were repeated three times.

H. Data Management Plan

The plan adopted for processing the large body of experimental data generated by the diverse components of this project was complex. The data management plan is presented in detail in two letters from the prime contractor

to the funding agency, dated May 25, 1983, and July 5, 1983. A summary of the steps involved in converting raw data to computerized records is given below.

Data were entered on the various source documents by those who did the work: interviewers filled out questionnaires during the interviews with cases and controls; sanitarians filled out environmental sampling forms as food specimens were sampled; laboratory technologists filled out lab cards at the completion of pertinent tests and procedures.

Data contained in these source documents were encoded by staff at the prime contractor's office who were trained for that purpose. An exception was the process for coding and proofing subcontractor's data; this was performed by the staff who did the work at each subcontractor's laboratory.

These handwritten code sheets were then keypunched at the computer services section of the University of Washington School of Oceanography under subcontract to the prime contractor. The resulting printouts were proofed 100% for consistency with their source documents; proofing was performed by someone in the prime contractor's staff other than the person who did the original coding.

Copies of those printouts were also forwarded to FDA for entry into its text edit system, WYLBUR. The resulting WYLBUR files were proofed by prime contractor staff against source documents until verified as correct.

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Then, data in WYLBUR were entered on-line into the Microbial Information System (MICRO-IS), a component of the National Institutes of Health Computer System.

MICRO-IS printouts were proofed for accuracy of conversion to the binary number system it employs, then were sent on magnetic tapes to the Academic Computer Center, University of Washington, where they were prepared for analysis using Scientific Programs for the Social Sciences (SPSS) programs.

This data flow system thus satisfied the contract requirement that all data generated by the project be entered in MICRO-IS, and at the same time produced data files for analysis by SPSS, the program preferred by the prime contractor.

I. Analytical and Statistical Methods

Statistical methods that were used were primarily descriptive. This approach to data analysis was chosen whenever possible in order to permit the data to speak for themselves. However, in numerous instances, especially in the case/control component of the study, statistical tests were done to substantiate what was apparent from review of the data.

Bar charts were used to display incidences and proportions, and confidence intervals were used to give a range of the possible values of the parameter of interest. Confidence intervals were not calculated when the

sample size was small or when the estimated proportion was small. All computed confidence intervals had a confidence coefficient of 0.95, meaning that there is 95% confidence that the true proportion lies within the given interval.

In many instances throughout the analysis it was informative to use contingency tables. In assessing associations between rows and columns in these tables, the usual chi-square statistic (27) was computed to determine strength of association when most of the cell counts were sufficiently large (5 or more). In some cases, it was appropriate to test for trend in a contingency table; in those instances the Armitage test for trend (27) was used. However, when data were sparse, no formal statistical tests were done.

Description of statistical and analytical methods of two components of the study are presented elsewhere in the report for convenience. The method used to determine the breakpoint between "susceptible" and "resistant" C. jejuni in the Kirby-Bauer test is presented in Results Section F., Results of antibiotic Susceptibility Testing. Likewise, the analytical and statistical methods employed in the case/control analysis are presented in Methods Section D., Case/Control Study.

V. RESULTS

A. Summary of Work Accomplished

Table 1 presents the final status of work performed on all scientific aspects of the project. In the table the actual work performed is compared to that projected in our original proposal submitted in response to RFP #223-81-7041.

Note that the total numbers of C. jejuni cases investigated was in the center of the range of projected totals. This occurred even though case investigation was shortened by two months due to delay in approval of the project questionnaire. Thus, data collection began in April 1982, rather than in February 1982, as originally proposed, and extended through September 1983.

Furthermore, note that the number of specimens taken from the environments of C. jejuni and Salmonella cases were below those projected. We originally projected three specimens per household for C. jejuni cases, but accomplished 2.15 specimens per household. This disparity was due to less than ideal compliance with stool collection by household members of cases.

With respect to the low number of Salmonella cases investigated and the low proportion of projected cultures that were taken from the homes of Salmonella cases, we noted a perceptible reluctance on the part of patients with Salmonella infections to have their cases fully investigated. We concluded that individuals with Salmonella infec-

Table 1

Summary of Work Accomplished

	Accomplished	Projected(*1)
C. jejuni cases investigated	218	165-250
C. jejuni controls interviewed	526	400-500
Salmonella cases investigated	72	100-150
Specimens taken from environment of:		
C. jejuni cases	468	500-750
C. jejuni controls	190	0
Salmonella cases	76	300-450
Food specimens cultured	1936	2000
Antibiotic susceptibility testing		
C. jejuni	>98%(*2)	100%
Salmonella	92.7%	100%
Plasmid analysis		
C. jejuni	>98%	50%
Salmonella	15%(*3)	0

(*1)Original projection contained in proposal submitted in response to RFP #232-1-7041.

(*2)Percentages refer to the percentages of all available isolates that were tested for antibiotics susceptibility and plasmids.

(*3)*Salmonellas* isolated from specimens that also cultured *C. jejuni* were tested for plasmids.

tions have preconceived ideas about salmonellosis which make them less willing to discuss details of their illness, and less willing to have interviewers come into their homes to collect further specimens from household members and the household environment.

Other aspects of work performed show very close attainment to projected goals. Note particularly that the number of food cultures represents 96.8 percent of the projected total of 2,000. In addition, the work provided by our subcontractors responsible for drug susceptibility testing and plasmid analysis encompassed virtually the entire stock of C. jejuni isolates that were available for testing. In the case of plasmid analysis, the scope of work was considerably greater than that projected.

B. Surveillance of Processor and Retail Foods

Table 2 summarizes results of food surveillance. 452 (23.3%) of the 1936 samples cultured during the 20 month period of surveillance were contaminated with Campylobacter jejuni, Salmonella sp., or Yersinia. C. jejuni was by far the most prevalent contaminant among the three.

Most C. jejuni contamination occurred in poultry. Almost 50% of samples from the processor were positive for C. jejuni whereas retail poultry showed about half of that positivity rate. C. jejuni was only rarely cultured from other species of meat.

Salmonella sp. were occasionally cultured from poultry,

Table 2

Overall Results of Food Surveillance
Feb. 1982-Sept. 1983

	(N)	Campylobacter jejuni	Salmonella sp.	C. jejuni & Salmonella	Yersinia
Poultry Processor	297	138(46.5)	14(4.7)[1]	30(10.0)[2]	1(0.3)
Retail Products					
Poultry	862	192(22.3)	30(3.5)	7(0.8)	11(1.3)
Beef	230	1 (0.4)	0	0	6(2.6)
Turkey	168	1 (0.6)	2(1.2)	2 (1.2)	1(0.6)
Pork	142	0	4(2.7)	1 (0.7)	2(1.3)
Lamb	37	0	0	0	0
Game Hens	29	4(13.8)	0	1 (3.4)	0
Rabbit	9	0	0	0	0
Duck	3	0	0	0	0
Goose	1	0	0	0	2(1.3)
Miscellaneous	151	2 (1.3)	0	0	
TOTALS	1936	338(17.5)	50(2.6)	41(2.1)	23(1.2)

[1]One processor sample cultured two Salmonella sp.

[2]Two processor samples cultured C. jejuni and two Salmonella sp.

[3]One pork sample cultured two Salmonella sp.

turkey, and pork. In almost half of samples in which Salmonella was found, C. jejuni was also cultured. S. typhimurium was the most frequent serotype encountered, it accounted for 22 of the Salmonella isolates. The other most frequent serotypes were S. heidelberg, 14 isolates; S. infantis, 13 isolates; S. litchfield, 12 isolates; S. blockley, 6 isolates; S. agona and S. derby, 5 isolates each; S. enteritidis, 4 isolates; S. anatum, S. indiana, S. schwarzengrund, and S. Thompson, 2 isolates each. Neither S. dublin nor S. cholarae-suis were encountered in specimens of food.

Yersinia was the least frequently cultured bacterial contaminant but was found more often than c. jejuni or Salmonella in specimens from beef.

Most of the miscellaneous specimens noted under retail products were work surfaces; the contamination rate for these surfaces was low. However, work surfaces in the poultry processor were frequently positive. A saw blade used to cut parts of the processor was cultured 50 times; C. jejuni was found in 28 specimens (56%, data incorporated into poultry processor line listing in Table 2).

It is notable that whereas C. jejuni contamination of retail poultry was less than half that of processor poultry products, Salmonella positivity rates, though much lower, remained nearly constant from processor to retail markets.

Sixteen of the Salmonellas isolates at the processor

were S. typhimurium. S. infantis was cultured 10 times, S. litchfield 8, S. blockley 5, S. agona 4, S. enteritidis and S. thompson, twice each.

Analysis of results of C. jejuni surveillance at the poultry processor produced several interesting observations. First, the period of the year during which poultry products had the highest rate of positivity for C. jejuni was July through October (see Figure 3, in which these data are presented graphically in juxtaposition with those from retail food sampling). In July 1982, the rate peaked at 79.2% (19 of 24 specimens positive); in October the positivity rate was 75.0% (18 of 24). In November, January, and March, products at the processor had the lowest C. jejuni positivity rates: 33.3%, 41.7% and 36.7%, respectively.

Furthermore, rates of C. jejuni contamination were not uniform throughout the processing chain. Figure 1 shows processor specimens divided according to sequence of handling. Specimens marked on the figure as "incoming birds" were cloacal swabs of individual birds soon after entry. This positivity rate of over 60% gives the best estimate of enteric carriage of C. jejuni by incoming poultry. Giblet specimens were taken from pooled visceral parts after evisceration, and show almost identical C. jejuni positivity as did cloacal swabs. C. jejuni contamination fell successively at the next two culturing stations, the chlorinated ice-water bath ("chlorine-washed") and the point

Figure 1

C. jejuni Contamination of Processor Products

Positivity Rates at Sequential Sites

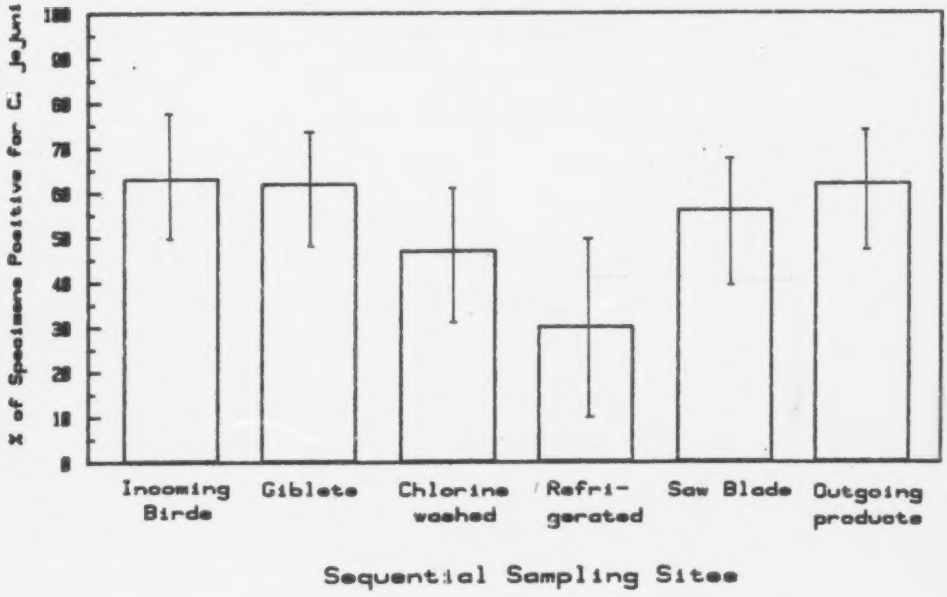
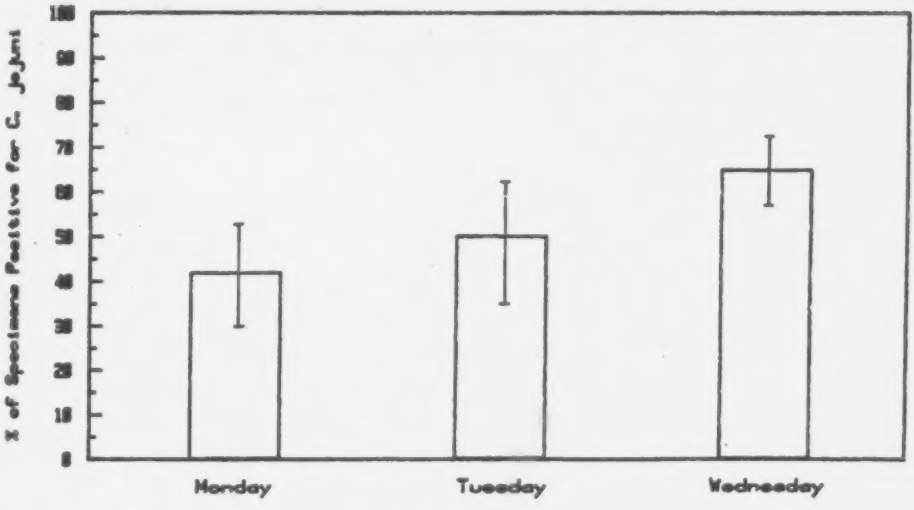


Figure 2

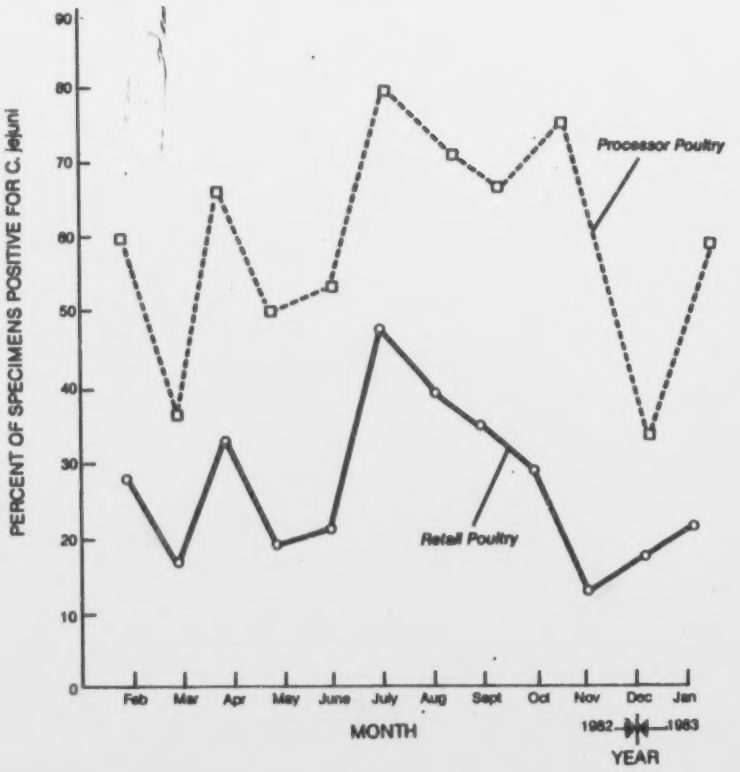
C. jejuni Contamination of Processor Products

Positivity Rate by Day Sample was Taken



Day of Week Sample Taken

Figure 3
Monthly Isolation Rates of C. *jejuni* In Processor and Retail Poultry



at which washed, refrigerated carcasses ("refrigerated") emerged from holding for final processing. C. jejuni contamination then was found to increase in specimens that had been completely processed and were ready for departure; the positivity rate was almost identical to that of incoming birds. Of note is the fact the saw blade used to prepare those products was positive for C. jejuni with the same frequency as the products themselves.

Further analysis of results within the processor revealed a trend toward increasing rates of C. jejuni contamination of products cultured from Monday through Wednesday (Figure 2). A consideration of possible explanations for this observation includes the following information. First, the processor is closed on Saturday, at which time a thorough clean-up and wash-down is routinely performed; secondly, fresh birds are processed each Monday, whereas during the week, products within the processing sequence are held, stored, and recycled according to production quotas. Thus, there is a progressively greater likelihood of culturing a recycled product rather than a fresh product as the week progresses.

In most instances the origin of products cultured at the processor, i.e. the farm where the bird was raised, was not known, but origin information was available for a minority of specimens. Among 19 specific farms that were identified as the origin for at least two poultry specimens, 17

(89.6%) were associated with at least one specimen positive for C. jejuni. These data, though sparse, suggest that contamination of poultry by C. jejuni is not a problem localized to a small proportion of commercial farms.

On the other hand, there was evidence of geographic variation in C. jejuni contamination of poultry sampled at the processor. On specimens for which the county of origin of the product was known, the majority were derived from Snohomish County, adjacent to King County to the north, and Pierce County, adjacent to the south. The positivity rates for C. jejuni of products from the two counties was different: 77% (57/76) for those from Snohomish County; 38.5% (25/65) for those from Pierce County. The reasons for this variation are unknown.

Several factors that could have affected the number of positive C. jejuni cultures at the processor were considered. Among these were hour of the day during which samples were taken and temperature of the products sampled. Rates of positive cultures were analyzed for each of these factors and no significant relationship was found.

One possible source of bias in results of culturing within the processor and in retail markets was that sampling was not random. The nature of the study design, which was the incorporation of food surveillance into an ongoing food inspection program, precluded the collection of samples of retail products throughout King County and within the poul-

try processor on a random basis. Interpretation of the results of the study must include a consideration of this potential source of bias. As an example, the SKCHD laboratory was not able to process samples on the weekend so that virtually all samples had to be taken on Monday through Wednesday. The sanitarians taking the samples predicted that a larger proportion of samples would be positive later in the week. This was confirmed in part by the rates shown in Figure 2. Thus, if the contamination rates continued to increase on Thursday and Friday, the estimates of C. jejuni contamination of processor products detected in the present study would be below the true rates.

In summary, results of surveillance culturing at the poultry processor revealed that C. jejuni was by far the most prevalent contaminant, with an overall positivity rate of 56.5%. Estimates of the rate of C. jejuni contamination of outgoing products (67.8%) was virtually identical to that of incoming birds (63.3%). The processing stage associated with the lowest contamination rate for C. jejuni (30%) was the point at which chlorine-washed carcasses emerged from holding at refrigerated temperature for 2-24 hours. There was evidence that most farms supplying poultry to the processor raised poultry contaminated by C. jejuni. Finally, the rate of C. jejuni contamination of processor products increased progressively from Monday (42.4%) through Wednesday (65.4%).

Table 2 presents the overall results of cultures performed at retail outlets. Among the meat items sampled, poultry was the only one to show substantial contamination by the bacterial pathogens that were specifically cultured for. Furthermore, C. jejuni was isolated from poultry products far more frequently than Salmonella sp. and Yersinia.

Among Salmonella serotypes encountered in retail meat samples, S. heidelberg was most prevalent among poultry products with 14 isolates. S. typhimurium accounted for five poultry isolates, S. litchfield 4; S. infantis, 3; S. anatum and S. enteritidis, 2 each. Four of the salmonellas contaminating pork products were S. derby.

Because of the predominance of the association between C. jejuni and retail poultry, further results of retail surveillance will focus on that phenomenon.

First, the C. jejuni contamination rate of retail poultry was analyzed by season of the year. Figure 3 shows the monthly curves of positivity rates of retail specimens juxtaposed with that of processor products for the 12-month period during which parallel observations are available. The general seasonal pattern at the two levels is quite similar, showing a summer-fall peak in C. jejuni contamination rates.

Next, factors within stores were analyzed to see whether C. jejuni was associated with selected types of poultry products, display areas, or conditions. There was

evidence that handling of poultry products after being received at the retail level increased the likelihood of C. jejuni contamination. Figure 4 shows that the C. jejuni positivity rate for poultry products that were primarily not handled at the retail level was 17.9%; that for products that for the most part were processed further at the stores was 33.0%. Gizzards, with a relatively low rate of C. jejuni contamination, were generally frozen in blocks of ice at processors, shipped, then thawed and packaged at retail outlets.

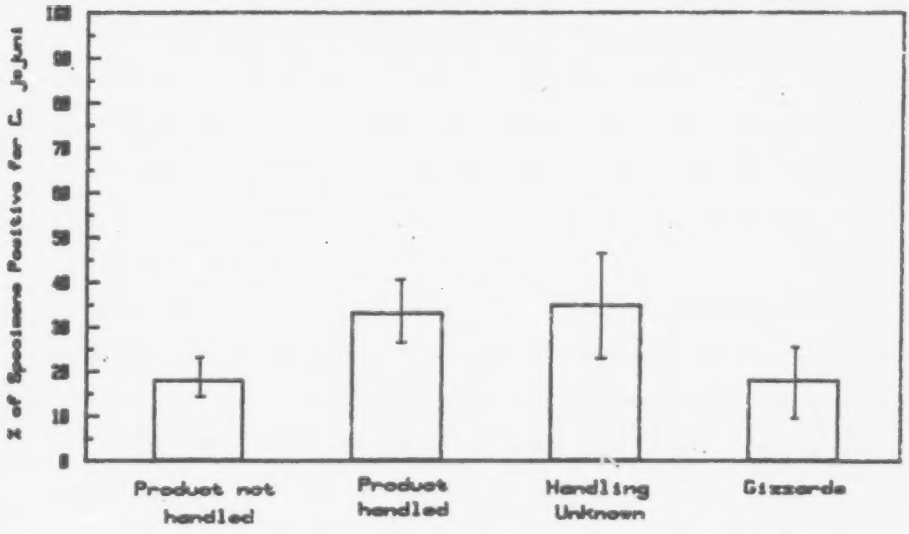
In consideration of the observation that products in the processor were less frequently positive after holding at refrigerated temperatures, retail poultry items were plotted as a function of the temperature of the item. No trend for C. jejuni contamination was observed.

The second stage in the analysis of results of retail surveillance was to seek "between-store" variability in C. jejuni contamination. Because of the large number of retail outlets involved in this phase of the food surveillance project and the small number of cultures taken at each, it was not possible to assess differences in contamination rates of poultry products at individual stores. It was possible however to assess C. jejuni contamination of poultry at stores grouped together as chains. Figure 5 shows that there was variation in C. jejuni contamination among such groups of retail outlets. Products from one chain in

Figure 4

C. jejuni Contamination of Retail Poultry

Positivity Rate According to Store Handling

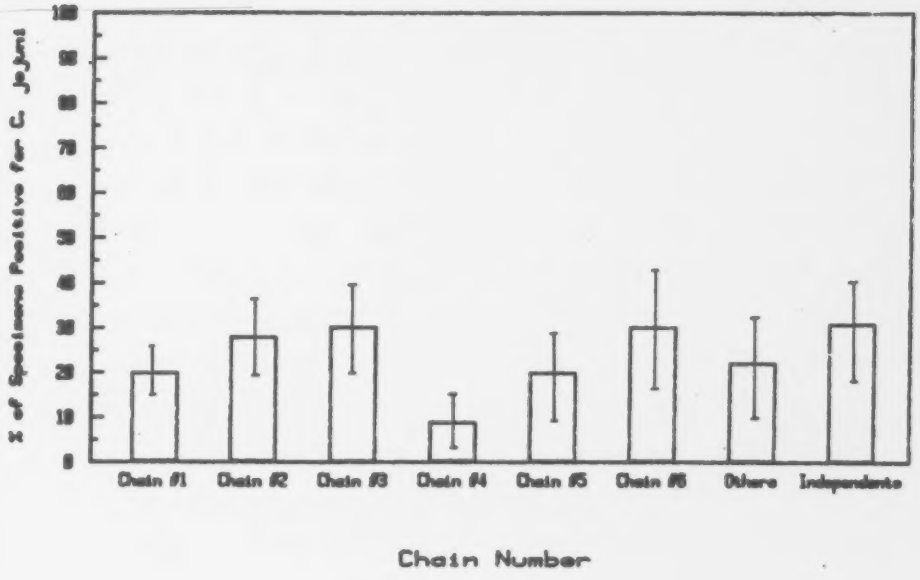


Type of Handling at Stores

Figure 5

C. jejuni Contamination of Retail Poultry

Positivity Rates at Retail Chains



particular (chain #4) had a very low positivity rate. Note that C. jejuni contamination of poultry at independent retail markets was in the range of contamination in the chain stores.

Another possible source of variation in C. jejuni contamination of poultry is the brand under which the product is marketed. Retail poultry products were marketed under a wide number of brand names, and C. jejuni positivity as a function of brand was examined. There was variability in contamination rates among the many brands of poultry, but no significance can be assigned to the observed differences because of lack of adequate samples within each brand.

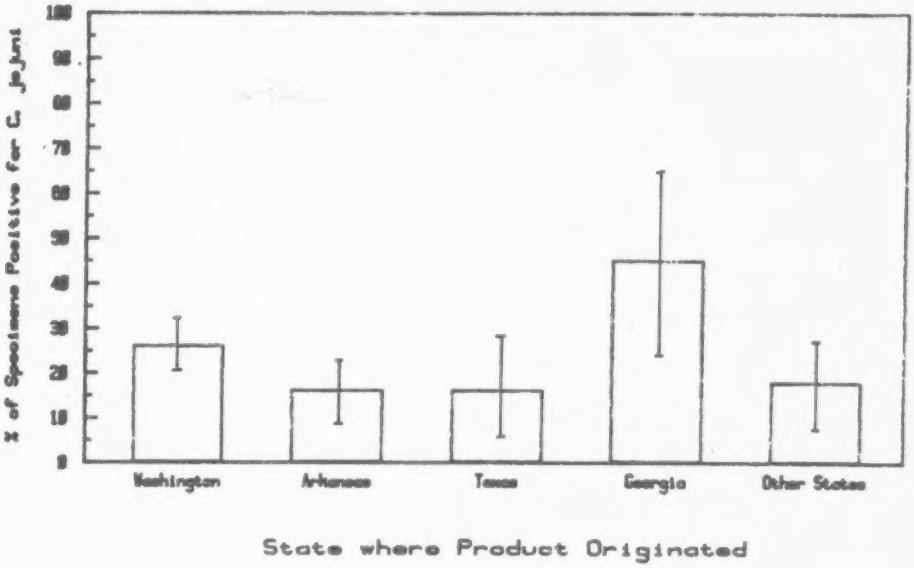
The third phase of analysis of retail food surveillance was to search for variability in C. jejuni contamination as a function of various classifications of origin of the products. First, the positivity areas of poultry processed in different states was examined (Figure 6). Most products that were sampled came from the state of Washington, but there were no significant differences in C. jejuni contamination according to state where the product originated.

There was no way to reliably assess the origin of retail products beyond the state where the product was processed. However, because of the unique role played by the poultry processor in the food surveillance component of the project, an effort was made to derive, for comparative purposes, the C. jejuni contamination rate of retail poultry

Figure 6

C. jejuni Contamination of Retail Poultry

Positivity Rate by State of Origin



products that were processed at that site. Retail products identified as coming from that specific processor were positive for C. jejuni of 27.0% (54/200); that positivity rate is not different from that of 22.3% for all retail poultry products.

It was also possible to identify, using U.S.D.A. identifying numbers, retail poultry products that originated at the two other large poultry processors in Western Washington. C. jejuni positivity rates of products from those processors were 29.9% (44/147) and 26.8% (26/97). Those rates are very similar to that (27.0%) of products from the processor that was targeted in the food surveillance system.

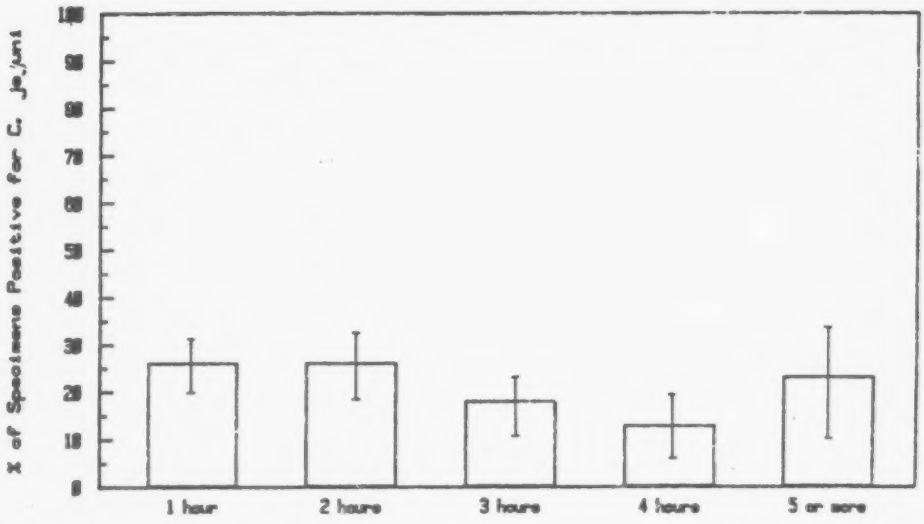
The final step in analysis of retail food surveillance was to determine whether there were factors which operated to confound the results that were obtained. The first variable examined for a confounding effect was the lag time between obtaining the specimen at the retail site and culturing it in the laboratory (Figure 7). Most specimens were plated for culture within three hours of being obtained. While there appears to be a decreasing trend in the positive samples for the first four hours, this trend fails to continue for hour five and the samples that were refrigerated overnight. No attempt has been made to adjust rates for time lag because it failed to show a consistent trend.

A variable that did exert an effect on the rate of C.

Figure 7

C. jejuni Contamination of Retail Poultry

Effect of Culture Lag on Positivity



jejuni contamination of retail poultry, as it did for processor specimens, was the day of the week on which the culture was obtained. A clear trend was observed toward increasing contamination as the week progressed from Monday through Wednesday (Figure 9). This trend is strikingly similar to that previously noted for sampling within the poultry processor (Figure 2). The reasons for this increasing rate of contamination were not apparent, but two known facts may be noted: first, many retail markets receive large deliveries of meat products early on Monday morning, prior to sampling that would have taken place that day; secondly, many stores clean their meat display cases prior to the beginning of work on Mondays. This combination of fresh products and clean display cases could account for less contamination on Mondays.

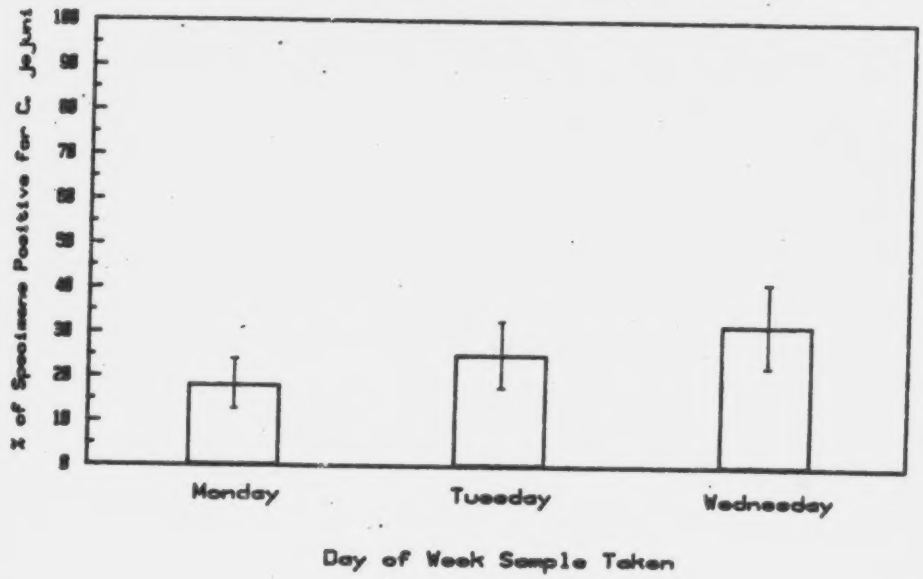
Although not completely understood, this trend to progressively greater C. jejuni contamination of retail poultry products during the week is a possible bias that may cause the rates observed in this study to underestimate the true contamination rates. Unlike day of the week, the hour of the day that a specimen was obtained failed to show an effect on rates of C. jejuni contamination of retail poultry.

In summary, contamination of retail poultry products by C. jejuni (22.3%) was significantly less than that noted at the processor (46.5%). Products that were handled at the store were more often contaminated than those simply dis-

Figure 8

C. jejuni Contamination of Retail Poultry

Positivity Rate by Day Specimen was Taken



played as received from the processor. No significant variability was noted in C. jejuni contamination rates between stores, or in products processed in various states or in those from different processors. This indicates that C. jejuni contamination of retail poultry is a general, rather than a localized phenomenon. Finally, as in the processor, C. jejuni positivity rates in retail poultry increased from Monday (18.1%) through Wednesday (31.6%)

C. ~~Epidemiological~~ and Clinical Description of Cases

The 225 C. jejuni index cases and 72 Salmonella index cases were analyzed with respect to basic descriptive epidemiological parameters. First, Group Health Cooperative patient enrollment data were used to derive age- and sex-specific incidence rates for these two infections in the GHC population during the period of surveillance (Table 3). The overall incidence rates were approximately 100 per 100,000 per year for C. jejuni (100 per 100,000 males, 110 per 100,000 females) and 40 per 100,000 (40 per 100,000 for both sexes) for salmonellosis. The pattern of age-specific incidence rates was similar in the two sexes.

Figure 9 shows that both C. jejuni and Salmonella infections had their highest incidence rates in children under one year of age. However, there was a second peak in C. jejuni incidence in the young adult years (ages 20-39) that was absent in salmonellosis.

Figure 10 shows the number of C. jejuni and Salmonella

Figure 9

Age Specific Incidence of *C. jejuni* and *Salmonella* Infection at GHC During the Period of Surveillance

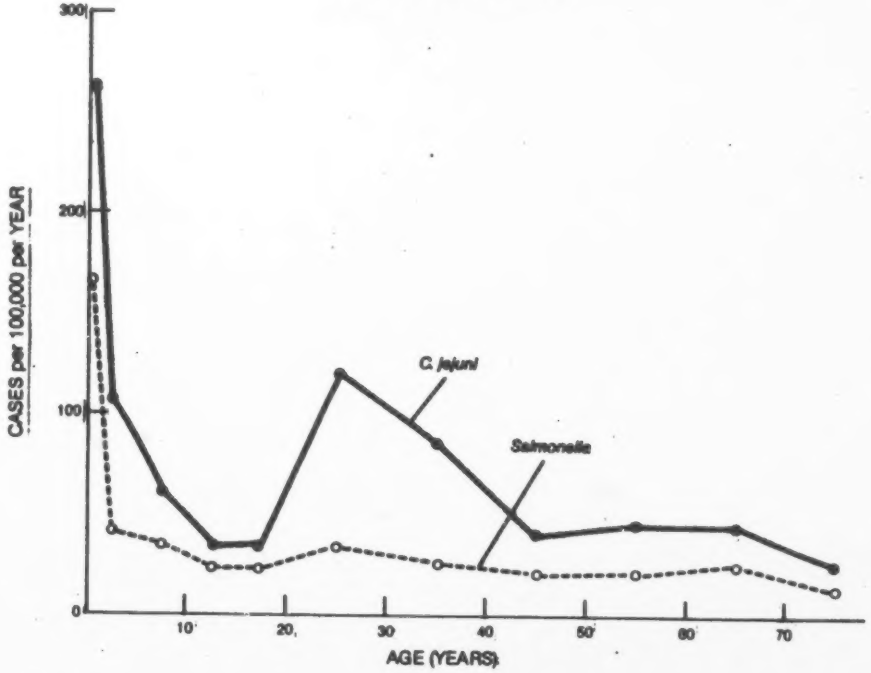
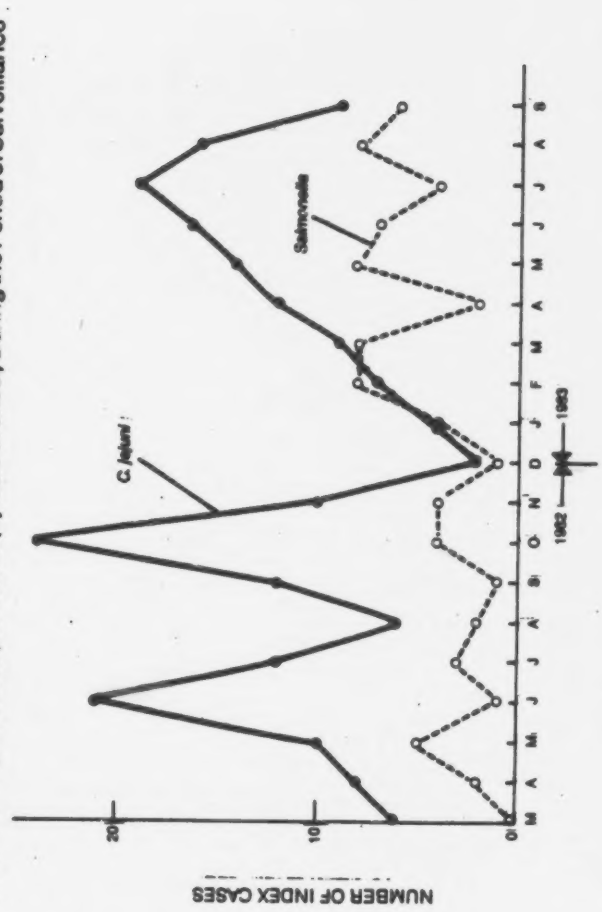


Figure 10
Number of Index Cases per Month (by date of onset) During the Period of Surveillance

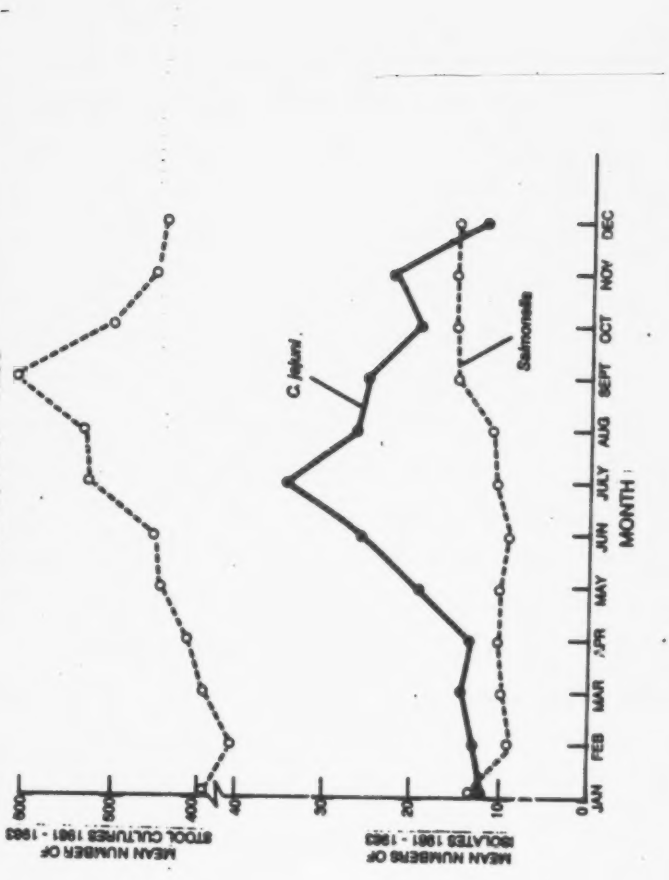


index cases plotted by month of onset during the period of surveillance. It should be recalled that for Salmonella cases the criteria for index cases was made more liberal beginning in January 1983. For C. jejuni cases, there were two peak months in 1982, and one in 1983. Each peak occurred during the summer-fall period. There were no obvious similarities between the monthly incidence of C. jejuni or Salmonella and the monthly frequency of isolation of those two species in the food surveillance system (Figure 3).

Figure 11 illustrates the seasonal frequency of C. jejuni isolation from patients at GHC in relation to the frequency with which stool cultures were obtained during the three year period 1981-83. A definite seasonal pattern is noted, with a summer-fall predominance in mean number of cases per month and in isolation rates of C. jejuni as a function of all submitted stool specimens. When viewed in this manner, the seasonal occurrence on C. jejuni cases in the GHC population shows a general similarity to the seasonal pattern of C. jejuni isolation in the food surveillance system (Figure 3).

Salmonella typhimurium was the most frequent serotype associated with human index cases as it was the most frequent food isolate; 34 cases showed that serotype. S. heidelberg, the most frequent serotype in retail poultry, accounted for 12 index cases. Other serotypes encountered in human cases more than twice were S. java, 7;, S. anatum and

Figure 11.
Mean Number of Stool Cultures plus *C. jejuni* and *Salmonella* Isolates per Month
GHC, 1981 - 1983


MEAN NUMBER OF STOOL CULTURES 1981 - 1983
MEAN NUMBERS OF ISOLATES 1981 - 1983
C. jejuni
Salmonella
JAN FEB MAR APR MAY JUN JULY AUG SEPT OCT NOV DEC
MONTH

S. mbandaka, 4 each; S. enteritidis, S. newport, S. oranienburg, and S. saintpaul, 3 each. Neither S. cholerae-suis nor S. dublin were encountered among isolates from humans.

Table 3 shows the frequency of symptoms associated with C. jejuni and Salmonella index cases. The clinical manifestations of the two infections were remarkably similar: almost all patients experienced diarrhea and cramps; and systemic symptoms such as fever, chills, headache, and myalgias were noted by the majority of both groups. Approximately half of both groups of patients reported bloody stools (hematochezia). Weight loss and arthralgia were reported more often by persons with C. jejuni infection than by those with Salmonella infection, but the differences were not large enough to be of practical importance.

In C. jejuni cases, there was a strong association of rash with age. 70% of children less than a year of age (7 of 10) with C. jejuni infection were reported to have a rash. The proportion of C. jejuni cases with rashes then diminished progressively as the age of the patients increased.

The total length of illness was greater among C. jejuni patients than among those with salmonellosis. In C. jejuni cases the mean length of illness was 13.52 $\pm$ 14.12 days (mean $\pm$ Std. dev.); that in Salmonella cases was 10.25 $\pm$ 5.82 days ($p=.014$, T-statistic with separate variance estimates).

Only 15 index patients with C. jejuni (6.7%) were

TABLE 3

Incidence of *C. jejuni* and *Salmonella* Infection During the 18 Month Period of Surveillance(*1)

C. jejuni Index Cases			*Salmonella* Index Cases		
Age (yrs)	Incidence (Cases/100,000/yr)		Age (yrs)	Incidence (Cases/100,000/yr)	
	Male	Female		Male	Female
<1	332.9	194.9	<1	237.8	97.6
1-4	107.1	113.3	1-4	10.7	68.0
5-9	64.3	57.8	5-9	45.9	67.5
10-14	23.7	41.1	10-14	15.8	24.7
15-19	39.1	33.4	15-19	15.6	25.1
20-29	119.6	124.7	20-29	19.3	34.0
30-39	83.1	95.1	30-39	25.3	29.7
40-49	41.1	44.6	40-49	23.5	22.3
50-59	27.8	62.1	50-59	7.2	31.1
60-69	47.2	45.2	60-69	15.7	32.2
≥70	26.1	26.8	≥70	0	17.4

(*1)Denominator data were GHC patient enrollment figures taken at the mid-point of the study.

hospitalized as a consequence of their infection. The longest length of hospital stay was 11 days, and 13 of the 15 remained in hospital for 5 days or less. Only 3 Salmonella index cases (3.5%) were ill enough to require hospitalization. There were no deaths associated with either illness during the surveillance period.

In summary, C. jejuni infections were more than twice as frequent than Salmonella infections at GHC during the period of surveillance. The highest incidence rates for both infections occurred in infants and young children, but for C. jejuni there was a second incidence peak in the young adult age group that was not seen with salmonellosis. The incidence of enteritis due to C. jejuni infection tended to be highest in the summer-fall period. The symptoms of the two illnesses were similar, with almost all patients experiencing diarrhea and cramps. Only a small fraction of patients with both infections were admitted to hospital and none died.

D. Results of Cultures Taken From the Home Environments of Cases

During interviews of C. jejuni cases and controls and Salmonella cases, arrangements were made to perform cultures of contacts of index cases, including household members, pets, and, if available, implicated food. 468 were taken in the home environments of C. jejuni cases: 46 (9.8%) were positive for C. jejuni. 190 cultures were performed in households of C. jejuni control

subjects, and none were positive. One specimen from a household of a C. jejuni case, and one from a control, grew Salmonella.

76 cultures were obtained from the home environments of Salmonella cases; 18 (23.7%) were positive. Family members of index cases of Salmonella more frequently had positive stool cultures (11/37=29.7%) than those of C. jejuni index cases (36/290=12.4%). Only a few specimens of food that might have been implicated in a case were available for culture in homes of cases; none of 10 food cultures from C. jejuni cases homes and none of 2 food cultures from homes of Salmonella cases were positive.

Table 4 shows stool culture positivity rates of various types of contact of C. jejuni and Salmonella cases. In households of C. jejuni index cases, siblings were most frequently culture positive; spouses or partners, least frequently positive. Among non-human contacts all 9 positive cultures came from specimens from 120 pets, a positivity rate of 7.5 percent. Comparisons between results of cultures of C. jejuni and Salmonella cases are difficult because the numbers taken in Salmonella cases households were small.

In summary, C. jejuni was found in approximately 10 percent of cultures taken from home environments of C. jejuni cases but the organism was not detected in controls or their home environments. All types of family contacts of C. jejuni cases were positive in proportions ranging from

Table 4

Symptoms and Signs of C. jejuni and Salmonella Infections

Symptom/Sign	C. jejuni (225 patients)		Salmonella (87 patients)	
	# Positive / # Responding	Percentage	# Positive / # Responding	Percentage
Diarrhea	214/217	98.6%	62/65	95.4%
Cramps	194/211	91.9%	62/71	87.3%
Weakness	184/210	87.6%	51/65	78.5%
Weight loss	174/203	85.7%	36/62	58.1%
Anorexia	169/215	78.6%	46/65	70.8%
Fever >100 F	158/198	78.4%	55/68	76.0%
>103 F	56/198	28.3%	18/68	26.5%
Chills	155/207	74.9%	48/64	70.6%
Headache	144/197	73.1%	43/65	66.2%
Myalgias	125/189	66.1%	36/63	57.1%
Nausea	132/208	63.5%	41/67	61.2%
Hematochezia	107/201	53.2%	30/62	48.4%
Dizziness	104/198	52.5%	29/63	46.0%
Arthralgias	67/203	33.0%	11/64	17.2%
Vomiting	55/215	25.6%	21/72	29.2%
Rash	26/211	12.3%	5/68	7.4%

approximately 5 percent for spouses and partners to approximately 25 percent for siblings of index cases. Pets were also occasionally positive (7.5%), but C. jejuni was not detected in food available for culture at the time of interview.

E. Outbreak Detection and Investigation

During the 18-month period of surveillance, only one outbreak of C. jejuni infection was detected. (In this section, "outbreak" is defined in traditional terms to mean a recognized incident in which two or more persons have the same disease with a time, place, and/or person association among those persons). The outbreak, which is presented in detail as Appendix B to this report, affected six culture-confirmed cases of C. jejuni infection between July 15 and August 3, 1983, and was traced to a commercial raw goat milk dairy. During that period, 38 total cases of C. jejuni infection were diagnosed in King County.

Four of the outbreak-related cases drank the implicated dairy's raw goat's milk, and two did not. The latter two, an employee of the implicated dairy and her infant son, experienced several potential exposures through the dairy, including direct and indirect contact with goat's manure, camping with the owner's children who were ill with diarrhea, and consumption of the dairy's yogurt.

A sampling of 10 goats from the implicated dairy (Dairy A) as well as from each of two other Puget Sound commercial

dairies (Dairy B and C) resulted in six positive samples (three each from Dairy A and B). Additionally, a relatively high level of mastitis (approximately 25%) was noted in Dairy A.

Characterization of goat and human isolates revealed the outbreak strain to be sensitive to ampicillin, tetracycline, streptomycin, and erythromycin, resistant to sulfasoxizole-trimethoprin, hippurate positive, plasmid negative, Lior serotype 36 and Penner serotypes 3,4,6, 13. Isolates from Dairy B and from humans who were ill during the outbreak period but who were not exposed to the goats or the milk from Dairy A were distinctly different from the outbreak strain.

During the entire two-year period from January 1982, through December 1983, which includes the 18-month period of C. jejuni case surveillance at GHC, the SKCHD Epidemiology Section epidemiologist reported 42 foodborne outbreaks, not counting the one noted above. Etiological agents diagnosed in those outbreaks were Clostridium perfringens in 7, Salmonella in 2, C. botulinum, Yersinia enterocolitica, and Shigella, in one each, histamine and monosodium glutimate in one each, and chemicals in two. In the remainder of outbreaks the etiologic agent was not determined.

One of the Salmonella-related outbreaks was caused by S. typhimurium and involved two persons who had consumed home-barbecued chicken. The other was caused by S.

enteritids. A refugee family from Laos purchased a pig, slaughtered and froze the carcass. After eating a portion homecooked, eleven of 18 persons eating pork were ill with typical symptoms of Salmonellosis. S. enteritidis was isolated from stools of twelve patients. The resulting investigation showed that both cross-contamination of food contact surfaces and undercooking of the pork by the stir-fry method were responsible for the outbreak.

F. Results of Antibiotic Susceptibility Testing

Results of susceptibility testing of Salmonella isolates are presented in Tables 5 and 6. The majority of Salmonella food isolates were resistant to erythromycin but susceptible to the other antibiotics that were tested (Table 5). Note that resistance to streptomycin and tetracycline was more prevalent in retail than in processor poultry. Salmonella isolates from cases and their contacts (Table 6) had susceptibility patterns that were generally similar to those of food isolates.

Campylobacter jejuni susceptibility testing required considerable preliminary work because techniques and conditions for determining drug susceptibilities of this organism have not been standardized. The first step in that process was to select and perfect a method to give reproducible minimal inhibitory concentration (MIC's) of the antibiotics of interest. The agar dilution method was selected for that purpose; conditions chosen for its use are described in the

Table 5

Results of Stool Cultures of Various Types of Contacts of *C. jejuni* and *Salmonella* Index Cases

Type of Contact	Number Positive/Number Cultured	
	C. jejuni Index Case	*Salmonella* Index Case
Spouse of partner	4/79 (5.1%)	4/ 6 (67 %)
Parent	13/92 (14.1%)	4/17 (23.5%)
Child	7/62 (11.3%)	0/6 (0 %)
Sibling	12/45 (26.7%)	3/6 (50 %)
Non-household	1/59 (1.7%)	0/5 (0 %)
Non-human	9/131 (6.9%)	7/36 (19.4%)

Table 5

Table 6

Susceptibility Testing(*1) Salmonella Isolates
From the Food Surveillance System

Antibiotic	Processor Poultry	Retail Poultry(*2)	Other Retail Meat(*3)	Totals
Ampicillin	28/28(*4)	41/42	6/6	75/76 (98.7)(*5)
Chloramphenicol	28/28	42/42	6/6	76/76 (100)
Erythromycin	3/28	17/42	1/6	21/76 (27.6)
Streptomycin	28/28	32/42	6/6	66/76 (86.9)
Tetracycline	28/28	29/42	6/6	63/76 (82.9)
Trimethaprim-Sulfamethoxazole	27/28	38/42	6/6	71/76 (93.4)

(*1)Testing performed by Kirby-Bauer method.

(*2)Includes results of specimens from turkeys and game hens.

(*3)All specimens isolated from pork.

(*4)Number susceptible/number tested.

(*5)Numbers in parentheses are percentages of all tested isolates that are susceptible.

Methods Section III.F.2, Agar Dilution Susceptibility Testing. The broth microdilution method, described in Methods Section III.F.3, was compared to the agar dilution method because of potential advantages of cost and efficiency. However, that method was abandoned because of inconsistent correlation with the results of agar dilution testing.

The final step in the general process of testing antibiotic susceptibilities of C. jejuni was to correlate the agar dilution technique with the disk diffusion (Kirby-Bauer) method (Methods Section III.F.4.) for a large number of isolates. The purpose of this correlation was to establish breakpoints for categorizing an organism as "resistant" or "susceptible" to a given antibiotic on Kirby-Bauer testing. For all drugs except erythromycin, MIC levels chosen to determine Kirby-Bauer breakpoints on scatter plots correlating the two methods were based upon achievable levels of the given antibiotic in human serum following a recommended dose of the drug. In the case of erythromycin, the conventional MIC endpoint for resistance $\geq$ 8 ug/ml was replaced by 16 ug/ml on the basis of the quality control strain S. aureus ATCC 25923 which consistently yielded an erythromycin MIC of 0.25 ug/ml in an aerobic atmosphere and an MIC of 0.5 or 1.0 ug/ml in the 5-7% CO_2 atmosphere of microaerophilic Campy-jars. The pH of the agar MIC plates was lowered by the CO_2 generated by the Campy-Pak™. The effect of CO_2 on in vitro susceptibility tests has been described by a number of

investigators and is attributed to the decreased ionization of erythromycin when the pH is lowered from 7.4 to 6.4 in a 5-7% CO_2 environment (38,39).

Campylobacter jejuni isolates from cases and their household contacts were chosen for testing by agar dilution and Kirby-Bauer methods. On analysis of the scatter plots of the logarithm (base 2) of the MICs versus Kirby-Bauer zone sizes for the six antibiotics of interest, two noteworthy observations were made. First, all isolates showed a minimal Kirby-Bauer zone when tested with trimethoprim-sulfamethoxazole (SXT), regardless of the MIC results. This false resistance to SXT on disk diffusion tests is presumably due to the effect of the heavy inoculum, adjusted to the turbidity of a 3.0 McFarland standard, which is 6-fold greater than the conventional Kirby-Bauer inoculum. It is well recognized that sulfonamide and trimethoprim susceptibility tests are affected by the inoculum density as well as by the presence of thymidine or other products of folate metabolism which enable bacteria to by-pass the action of these drugs. In this study, the addition of either lysed horse blood or thymidine kinase had no effect on C. jejuni SXT MIC's nor on the false resistance in Kirby-Bauer tests. Sulfonamide susceptibility tests are invalidated by a heavy inoculum which may contain enough p-aminobenzoic acid to inactivate the drug. If inocula are too heavy, the zones are not simply reduced, they disappear completely (40).

Secondly, with the remaining five antibiotics, the regression lines correlating results of the two testing methods did not fit the data sufficiently well to allow their use in determining Kirby-Bauer cut-off points.

Consequently the technique schematically presented in Figure 12 was chosen to determine Kirby-Bauer breakpoints. For each antibiotic, line A was drawn to separate sensitive and resistant organisms based on achievable serum levels and MICs. Then line B was drawn so as to minimize the number of isolates that would be misclassified upon analysis of Kirby-Bauer results, in comparison to MIC testing.

The scatter plots for the five antibiotics for which Kirby-Bauer testing was satisfactory are given in Figures 13 through 17. In interpreting these figures it should be pointed out that each point represented by a cross may represent more than one observation.

According to the plots in Figures 13 through 17, the percentage of isolates misclassified by Kirby-Bauer testing were less than 2 percent for each of the five antibiotics. This low error rate was considered acceptable for purposes of this study.

A final cautionary statement must be made prior to presenting results of antibiotic susceptibility testing of C. jejuni. MIC testing for food isolates was not performed under the terms of this contract. Hence, susceptibility patterns for C. jejuni isolated from food products can only

FIGURE 12
METHOD FOR DETERMINING KIRBY-BAUER BREAKPOINTS FOR **C. jejuni**

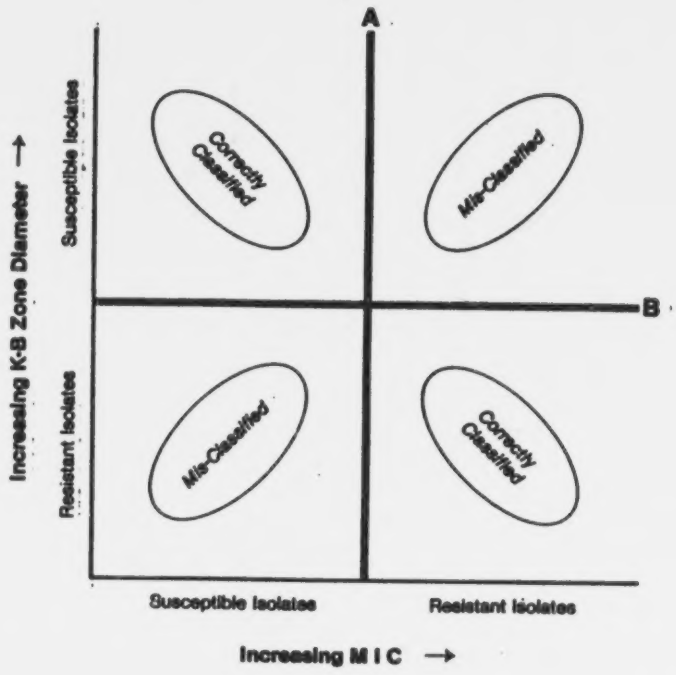


FIGURE 13
SCATTER PLOT - AMPICILLIN

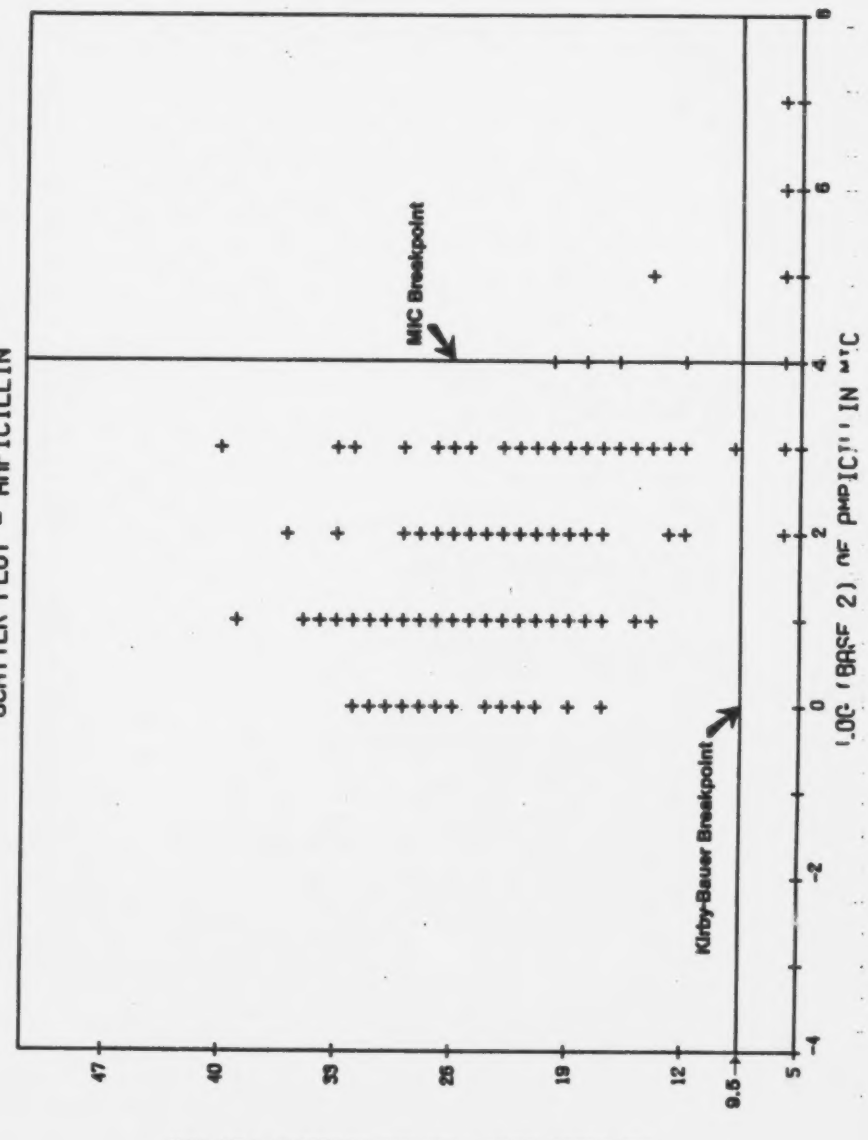


FIGURE 14
SCATTER PLOT - CHLORAMPHENICOL

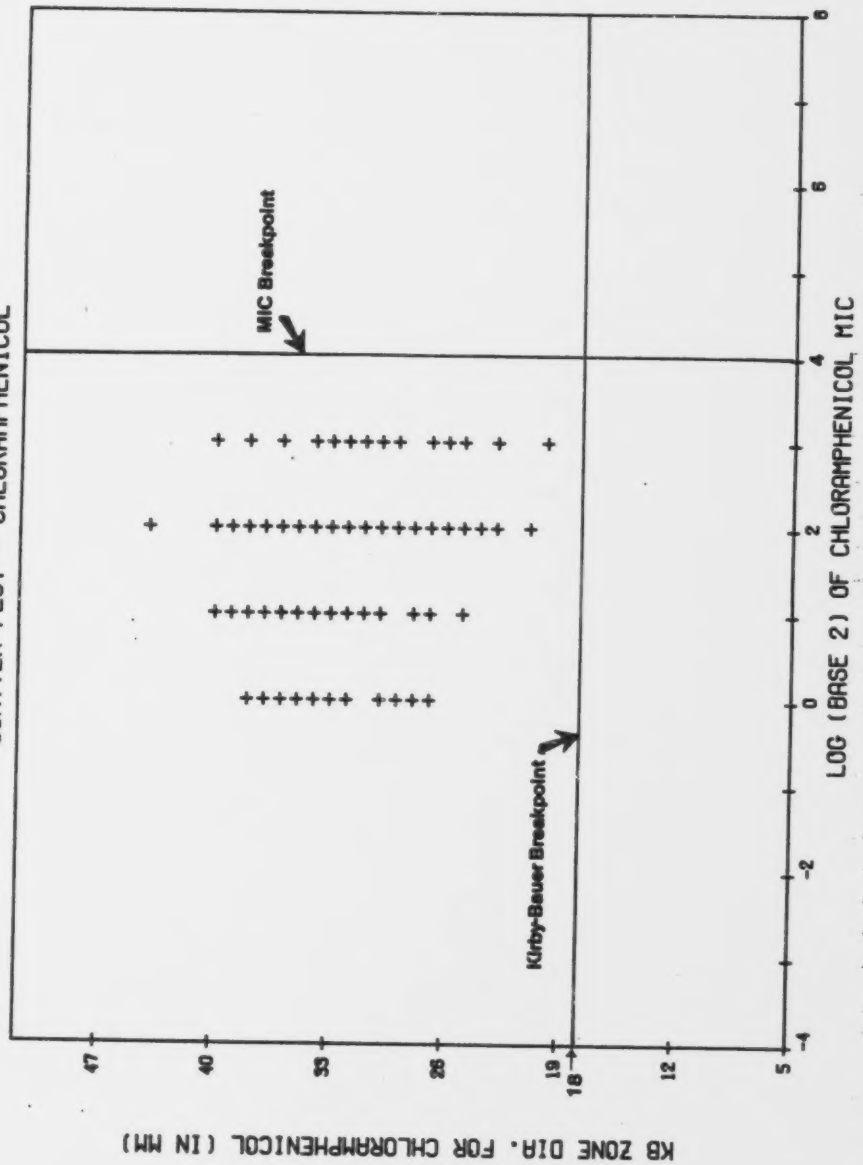


FIGURE 15
SCATTER PLOT - ERYTHROMYCIN

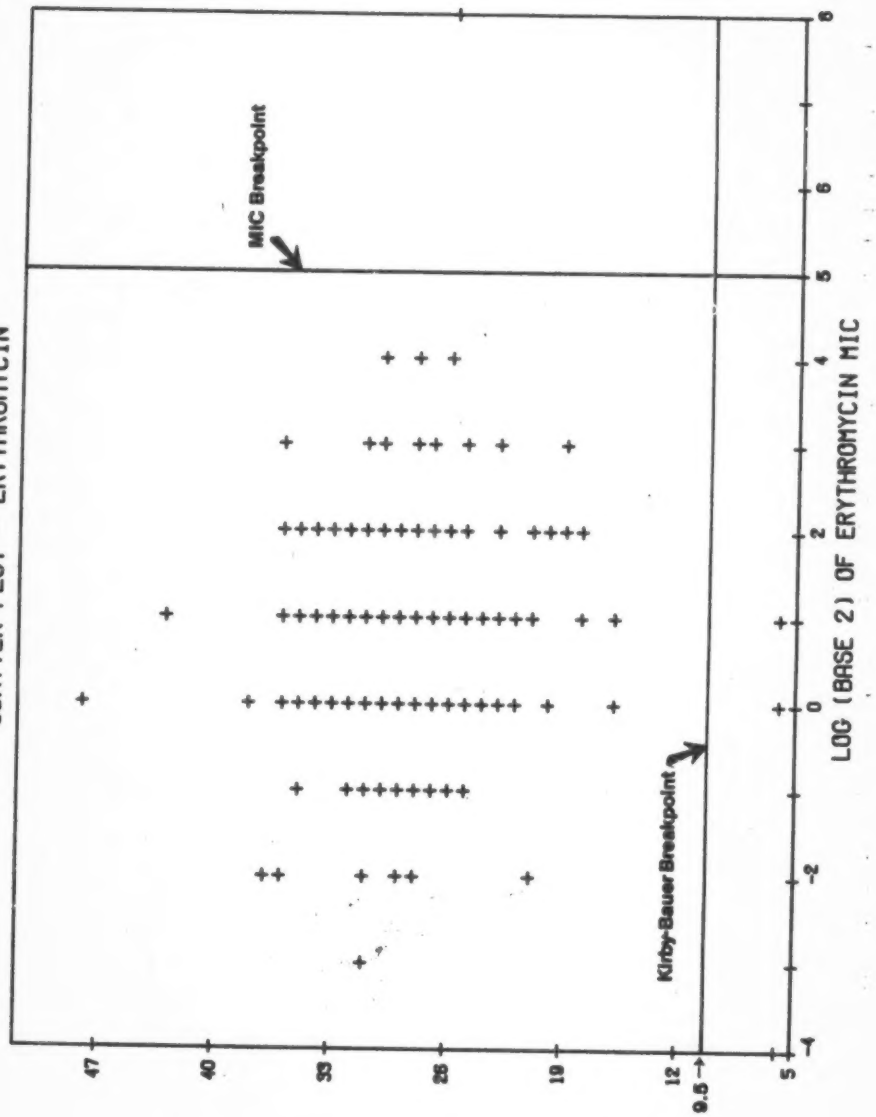


FIGURE 16
SCATTER PLOT - STREPTOMYCIN

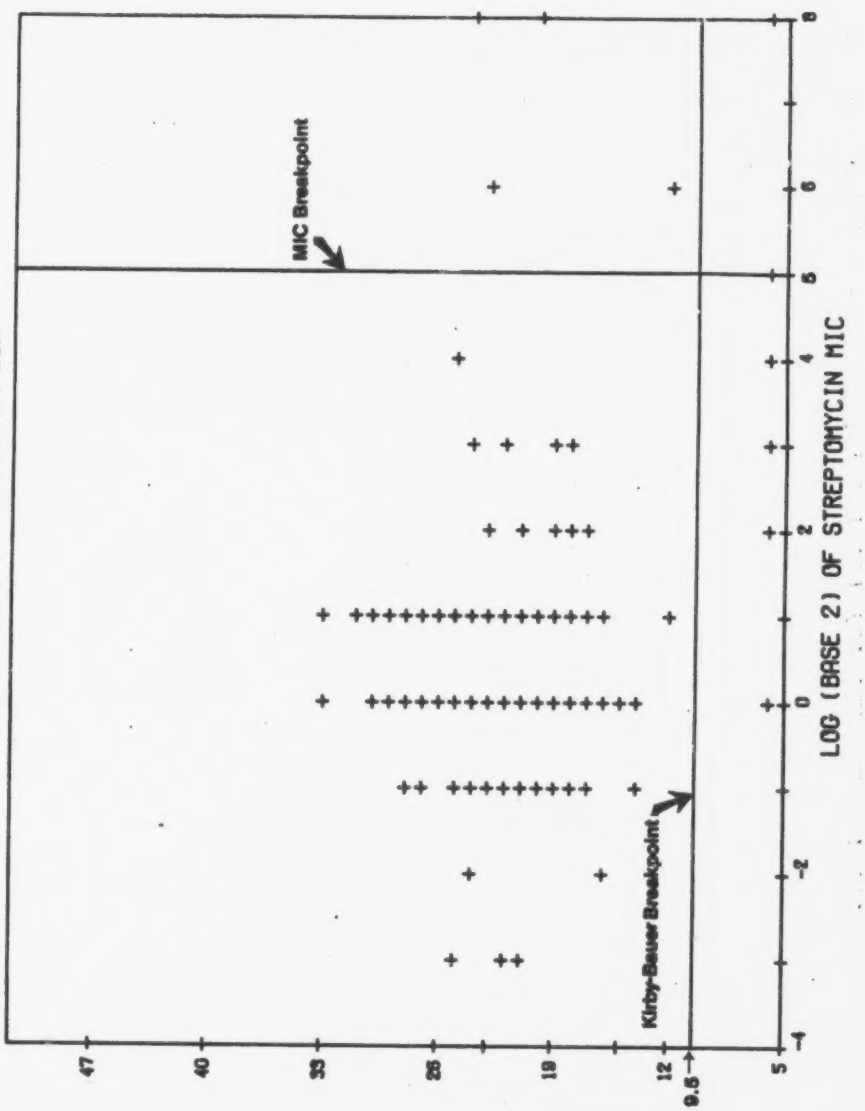
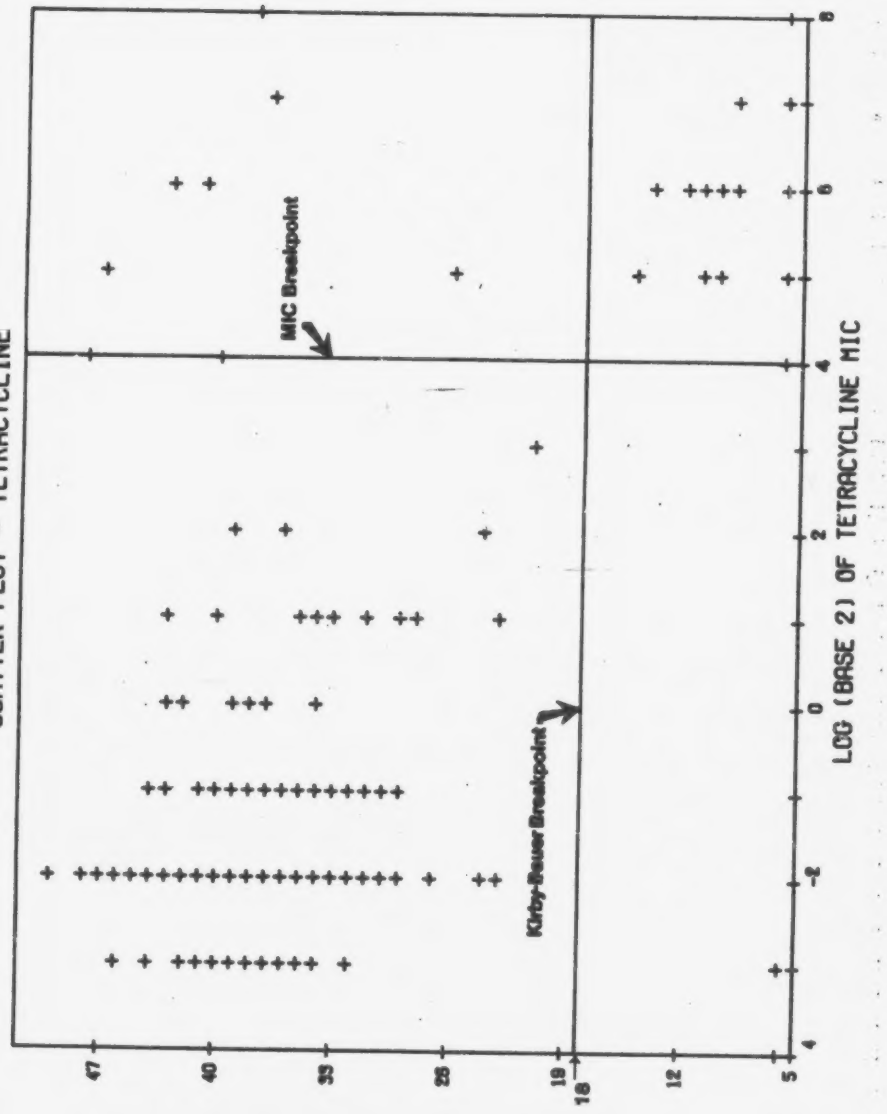


FIGURE 17
SCATTER PLOT - TETRACYCLINE



be determined using Kirby-Bauer zone diameter breakpoints as defined by testing of isolates from humans. In order to increase confidence in the interpretation of Kirby-Bauer testing of food isolates, Kirby-Bauer zone sizes of food isolates were compared directly to those of human isolates. For the five antibiotics ampicillin, chloramphenicol, erythromycin, streptomycin, and tetracycline, there were no differences in the distribution of Kirby-Bauer zone diameters between human and food isolates. Nevertheless, comparisons between susceptibility results of human and food C. jejuni isolates should be made with caution.

The frequencies of resistance to the antibiotics of interest among C. jejuni isolates from the food and case surveillance systems are given in Tables 7 and 8. When chicken isolates were divided into those associated with processor and retail products, there was a greater prevalence of resistance among retail products to four of the five antibiotics that were tested (Table 7). One-third of retail poultry isolates were resistant to tetracycline, a proportion very similar to that of human isolates (29.7%, Table 8) and household pets. In fact, frequencies of resistance to single antibiotics among isolates from humans, retail food, and pets were generally similar.

One possible explanation for the observation that C. jejuni isolates from processor products showed less antibiotic resistance than those from retail poultry was that there

Table 7

Susceptibility Testing(*1) of Salmonella Isolates from 114 Cases and Contacts

Antibiotic	Susceptible Isolates	Resistant Isolates
Ampicillin	106 (93.0)(*2)	8 (7.0)
Chloramphenicol	107 (93.9)	7 (6.1)
Erythromycin	42 (36.8)	72 (63.2)
Streptomycin	112 (98.2)	2 (1.8)
Tetracycline	100 (87.7)	14 (12.3)
Trimethoprim-Sulfamethoxazole	112(98.2)	2 (1.8)

(*1)Testing performed by Kirby-Bauer method.

(*2)Numbers in parentheses are percentages of isolates that are susceptible and resistant.

Table 7

Table 8

Susceptibility Testing of C. jejuni Isolates from the Food Surveillance System

Antibiotic	Number Resistant/ Number Tested (%)		
	Processor	Retail Poultry	All Isolates
Ampicillin	0/162 (0%)	20/195 (10.3%)	20/368 (5.4%)
Chloramphenicol	0/162 (0%)	0/195 (0%)	0/368 (0%)
Erythromycin	1/162 (0.6%)	10/195 (0%)	11/368 (3.0%)
Streptomycin	15/162 (8.6%)	26/195 (13.3%)	40/368 (10.9%)
Tetracycline	17/162 (10.5%)	64/195 (32.8%)	82/368 (22.3%)

is variation in antibiotic susceptibility of isolates from different geographic regions. Since the processor products all derived from poultry grown in Western Washington, it could be hypothesized that this population of poultry had less resistant C. jejuni than populations from other regions, which when counted among retail specimens, would inflate the proportion of resistant C. jejuni isolates in the entire pool of retail poultry.

Table 9 shows that for retail poultry isolates of C. jejuni for whom the state of origin were known, those from Washington showed a greater proportion of totally susceptible strains than those from other states. The difference remains significant even when the isolates from Georgia poultry, all of which were resistant to at least one antibiotic, were removed from the analysis. Among all 88 isolates possessing some degree of resistance, 64 (77.7%) were resistant to tetracycline.

A more comprehensive portrayal of antibiotic resistance of C. jejuni is given in Tables 10 and 11 by the presentation of frequencies of the patterns of antibiograms among isolates. Approximately half of human and retail food isolates were susceptible to all tested antibiotics, but three-quarters of processor poultry isolates were totally susceptible.

Tetracycline resistance was the most frequent single drug resistance encountered. In addition, a small propor-

Table 9

Susceptibility Testing of C. jejuni Isolates from Cases and Household Contacts

Antibiotic	Number Resistant/ Number Tested (%)	
	Human Isolates	Pet Isolates
Ampicillin	15/276 (5.4%)	3/31 (9.7%)
Chloramphenicol	0/276 (0%)	0/31 (0%)
Erythromycin	2/276 (0.7%)	1/31 (0.7%)
Streptomycin	22/276 (7.9%)	10/31 (32.3%)
Tetracycline	82/276 (29.7%)	9/31 (29.0%)
Trimethoprim-Sulfamethoxazole	25/276 (9.0%)	5/31 (16.1%)

Table 9

Table 10

Antibiotic Susceptibility of C. jejuni Isolates from Retail Poultry of Different Geographic Origin

State of Origin	Number of Isolates	Number Susceptible	Number Resistant	
			one drug	multiple drugs
Washington	143	88 (61.5%)	38 (26.6%)	17 (11.9%)
Arkansas	18	8 (44.4%)	8 (44.4%)	2 (11.1%)
Georgia	8	0 (0 %)	7 (87.5%)	1 (12.5%)
Texas	7	3 (42.9%)	3 (42.9%)	1 (14.3%)
Others	19	8 (42.1%)	7 (36.8%)	4 (21.0%)

Table 10

Table 11

Campylobacter jejuni Antibiograms Among Isolates from the Poultry Processor and Retail Chicken

Antiobitic Resistance Pattern(*1)					Poultry Processor n=162	Retail Chicken n=195
A	C	E	ST	T		
-(*2)-		-	-	-	125 (77.2%)	107 (54.9%)
-	-	-	-	R(*2)	13 (8.0%)	43 (22.1%)
-	-	-	R	-	9 (5.6%)	7 (3.6%)
-	-	R	-	-	0 (0%)	2 (1.0%)
R	-	-	-	-	10 (6.2%)	11 (5.6%)
-	-	-	R	R	4 (2.5%)	8 (4.1%)
R	-	-	-	R	0 (0%)	6 (3.1%)
-	-	R	R	-	1 (0.6%)	3 (1.5%)
R	-	-	R	-	0 (0%)	1 (0.5%)
-	-	R	R	R	0 (0%)	5 (2.6%)
R	-	-	R	R	0 (0%)	2 (1.0%)

(*1)A=ampicillin, C=chloramphenicol, E=erythromycin, St=streptomycin, T=tetracycline

(*2) -equals susceptible, R equals resistant

tion of C. jejuni isolates from all groups was resistant to streptomycin, ampicillin, and (among humans and pets) to SXT.

Patterns of multiple drug resistance were not frequent. Only 18 human isolates (6.3%) were resistant to two or more antibiotics; in all but one of those tetracycline resistance was included in the resistance pattern. Likewise, 25 retail chicken isolates (12.8%) were multiply resistant, with tetracycline resistance occurring among 21 of those 25 isolates. Only 3.1 percent of processor poultry C. jejuni isolates showed multiple antibiotics resistance.

Among the 13 C. jejuni isolates from all sources that were resistant to three or four antibiotics, the antibiograms of all 13 included tetracycline and streptomycin resistance.

G. Results of Plasmid Analyses

1. Screening C. jejuni isolates for plasmids

The results of plasmid testing of C. jejuni isolates from the study are summarized in Table 12. 661 isolates were screened; 212 (32.1%) contained plasmids. Of C. jejuni isolates containing plasmid DNA, 180 (84.9%) showed a single plasmid, 24 (11.3%) contained two, and 8 (3.8%) had 3 plasmids.

Among the groups of isolates shown in Table 13, a difference was noted in frequency of plasmid carriage between processor products and retail chicken; retail poultry products were over two and one-half times likely to contain one

Table 12

Campylobacter jejuni Antibiograms Among Isolates from Humans (index cases plus contacts) and Household Pets

Antibiotic Resistance Pattern(*1)						Cases, Contacts n=276	Pets n=31
A	C	E	St	Sx	T		
-(*2)-		-	-	-	-	161 (58.3%)	10 (32.3%)
-	-	-	-	-	R(*2)	65 (23.6%)	4 (12.9%)
-	-	-	-	R	-	16 (5.8%)	4 (12.9%)
-	-	-	R	-	-	7 (2.5%)	6 (19.3%)
R	-	-	-	-	-	9 (3.3%)	1 (3.2%)
-	-	-	-	R	R	7 (2.5%)	1 (3.2%)
-	-	-	R	-	R	2 (0.7%)	2 (6.4%)
R	-	-	-	-	R	3 (1.1%)	1 (3.2%)
-	-	R	R	-	-	1 (0.3%)	0 (0 %)
R	-	-	R	-	-	0 (0 %)	1 (3.2%)
R	-	-	R	-	R	3 (1.1%)	0 (0 %)
-	-	-	R	R	R	1 (0.3%)	0 (0 %)
-	-	R	R	R	R	1 (0.3%)	1 (3.2%)

(*1)A=ampicillin, C=chloramphenicol, E=erythromycin, St=streptomycin, Sx=trimethoprim-sulfamethoxazole, T=tetracycline.

(*2) -equals susceptible, R equals resistant

Table 13

Plasmid Carriage in *C. jejuni* Isolates

Number of Plasmids per Isolate	Origin of *C. jejuni* Isolates			
	Processor Products n=160	Retail Poultry n=199	Humans n=271	Pets n=31
None	182 (80 %)	121 (60.8%)	180 (66.4%)	20 (64.5%)
1	28 (17.5%)	63 (31.7%)	81 (29.9%)	8 (25.8%)
2	4 (2.5%)	11 (5.5%)	7 (2.6%)	2 (6.5%)
3	0 (0 %)	4 (2.0%)	3 (1.1%)	1 (3.2%)

Table 13

or more plasmids than processor poultry products (x^2 = 15.38). The proportion of human isolates containing plasmids was similar to that of retail poultry products.

Plasmids carried by C. jejuni ranged in size from 2.0 to 162 kilobases. There were two peaks in the size distribution; one between 40-50 kilobases; the other between 80-90 kilobases. Considerable size variation was encountered among the plasmids of C. jejuni isolates, and there appeared to be no plasmid type common to all C. jejuni. Furthermore, there were no differences in size or distribution of plasmids between hippurate positive and hippurate negative strains, indicating that C. jejuni and C. coli share a common pool of extrachromosomal elements.

2. Plasmid Carriage and Antibiotic Susceptibility

Tables 14,15, and 16 portray the relationship between plasmid carriage and antibiotic resistance in C. jejuni isolates from processor products, retail poultry, and humans. Several trends were apparent. First, C. jejuni isolates that showed no antibiotic resistance were likely not to carry plasmids; only 36 (9.3%) of 387 totally susceptible isolates in all three groups contained plasmid DNA. Secondly, there was a strong correlation between tetracycline resistance and plasmid carriage. Among 158 isolates from the three groups that possessed resistance to tetracycline either alone or together with resistance to other antibiotics, 147 (93%) contained one or more plasmids.

Table 14

Relationship Between Antibiogram and Plasmid Carriage in *C. jejuni* Isolates from Processor Products

Resistance Pattern(*1)	Plasmids per Isolate		
	None	One	Two
No resistance	108	13	2
Tetra. resistance	0	12	1
Strep. resistance	9	0	0
Amp. resistance	6	3	1
Tet., Strep. resistance	3	0	0
Strep., Erythro. resistance	0	0	0

(*1)Antibiotics tested: ampicillin (Amp.), chloramphenicol, erythromycin (Erythro.), streptomycin (Strep.), tetracycline (Tetra.).

Table 15

Relationship Between Antibiogram and Plasmid Carriage in *C. jejuni* Isolates from Retail Poultry

Resistance Pattern(*1)	Plasmids Per Isolate			
	None	One	Two	Three
No resistance	102	5	0	0
Tetra. resistance	1	38	4	0
Amp. resistance	10	1	0	0
Strep. resistance	4	2	1	0
Erythro. resistance	0	1	1	0
Tetra., Strep. resistance	0	6	1	1
Tetra., Amp. resistance	0	5	1	0
Strep., Erythro. resistance	1	2	0	0
Strep., Amp. resistance	1	0	0	0
Tetra., Strep., Erytho resistance	1	0	1	3
Tetra., Strep., Amp. resistance	0	1	1	0

(*1)Antibiotics tested: ampicillin (Amp.), chloramphenicol, erythromycin (Erythro.), streptomycin (Strep.), tetracycline (Tetra.).

Table 16

Relationship Between Antibiogram and Plasmid Carriage in *C. jejuni* Isolates from Humans

Resistance Pattern(*1)	Plasmids Per Isolate			
	None	One	Two	Three
No resistance	141	15	0	1
Tetra. resistance	3	57	5	0
TMP-SXT resistance	15	1	0	0
Amp. resistance	8	1	0	0
Strep. resistance	7	0	0	0
Tetra., TMP-SXT resist.	1	3	1	2
Tetra., Amp. resist.	0	3	0	0
Amp., Strep. resist.	3	0	0	0
Erythro., Strep. resist.	0	1	0	0
Strep., Tetra. resist.	1	0	0	0
Tetra., Strep., TMP-SXT resist.	0	0	1	0
Tetra., Strep., TMP-SXT, Erythro. resist.	1	0	0	0

(*1)Antibiotics tested: ampicillin (Amp.), chloramphenicol, erythromycin (Erythro.), streptomycin (Strep.), tetracycline (Tetra.), trimethoprim-sulfamethoxazole (TMP-SXT).

Plasmids from tetracycline-resistant C. jejuni tended to have sizes that clustered in a relatively narrow range, as indicated in Table 17. This relative homogeneity of plasmid size was not found in plasmids carried by C. jejuni in isolates that had resistance patterns that did not include tetracycline resistance: one isolate from a human that was resistant to TMP-SXT had a 3.0 kilobase plasmid; another, resistant to streptomycin and erythromycin, had a 143 kilobase plasmid. From the retail poultry group, a C. jejuni strain resistant to streptomycin and erythromycin had a 119 kilobase plasmid; another, resistant to ampicillin had a 124 kilobase plasmid.

Tables 14 through 16 show that there was no correlation between C. jejuni plasmid carriage and resistance to any tested antibiotic except tetracycline. A small proportion (6/34=17.6%) of ampicillin-resistant isolates from all groups that did not also show tetracycline resistance, did contain plasmids.

3. Conjugal Transfer of Tetracycline Resistance

31 tetracycline resistant isolates harboring plasmids ranging in size from 42 to 133 kilobase were tested for their ability to conjugally transfer the tetracycline resistance phenotype. Only a single isolate, containing a 133 kilobase plasmid, failed to demonstrate plasmid transfer. Frequencies of transfer ranged from $5x10^{-3}$ to $5x10^{-9}$ transconjugants per input donor cell. All transconjugants contained plasmids. Although several

Table 17

Molecular Size of Plasmids Carried by C. jejuni Isolates that were Resistant to Tetracycline

Origin of Isolates	Number of Isolates(*1)	Plasmid Size in Kilobases (mean ± St. Dev.)
Poultry processor	12	57.0 ± 24.5
Retail poultry	38	53.3 ± 13.5
Humans	57	50.4 ± 10.8

(*1)Isolates that contained only one plasmid

Table 17

of the isolates tested demonstrated resistance to other antimicrobials, transfer of other antibiotic markers in addition to tetracycline, such as erythromycin, was not observed for any of the isolates examined. Since the recipient strain appears to harbor a chromosomal beta-lactamase gene, the transfer of ampicillin resistance could not be assessed. Eleven of the plasmids, their sources and their frequencies of conjugation are shown in Table 18.

4. Restriction Endonuclease Analysis of R-Factor DNA

31 tetracycline R-factors ranging in size from 40 to 58 kilobase were cleaved with the restriction endonucleases BcII, BglII, and HincII. The HincII digests for the plasmids were quite similar, each demonstrating 2 large and 2 small fragments (data not shown). However, 18 distinct banding patterns were observed for each of the BcII and BglII enzymes. The BcII and BglII fragment patterns for six of the plasmids are shown in Figure 18. The BglII restriction profile of pFKT1000 from the simian isolate PS793 is included for comparison. Three restriction fragments (indicated by arrows) appeared to be conserved in 28 of the 31 plasmids examined. Despite the diversity, all fragments demonstrated homology with a whole plasmid DNA probe prepared from the R-factor of C. jejuni PS1025 (pFKT1025), a tetracycline resistant clinical isolates.

5. Relationship of Campylobacter R-Factors to the Tetracycline R-Factors of Enterobacteriaceae

This same plasmid (pFKT1025) was hybridized to a South-

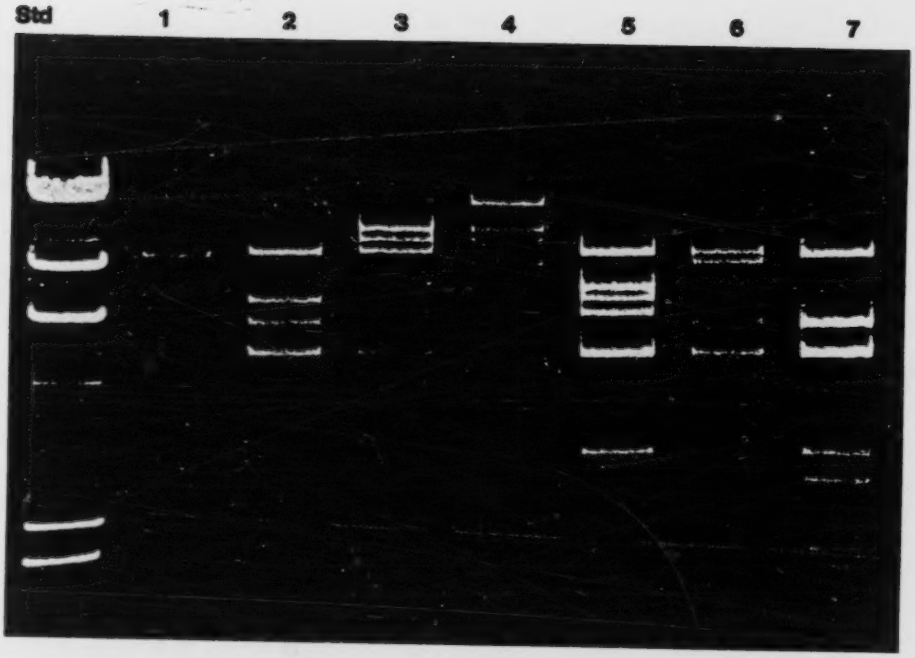


Figure 18. BGL II restriction endonuclease digests pf **C. jejuni** plasmids separated on 0.8% agarose gels. Std = molecular weight standards: Hind III digest of phageLambda. Lanes 2, 3, and 5 contain fragments of plasmids from **C. jejuni** isolates; Lanes 4, 6, 7, from humans. Lane 1 fragments are from an isolate from a Cynomologous monkey.

Table 18

Size, Tetracycline MIC, Frequency of Transfer and Source of Plasmid-Containing Isolates of C. jejuni

Strain #	Plasmid Size(*1)	Tet MIC(*2)	Freq of Transfer(*3)	Source
1	48	64	$4.3x10_{-4}$	Poultry
2	44	128	$1.8x10_{-7}$	Poultry
3	53	64	$1.3x10_{-7}$	Human
4	65	128	$1.8x10_{-5}$	Human
5	45	32	$4.5x10_{-7}$	Poultry
6	42	32	$4.6x10_{-7}$	Poultry
7	42	< 8	N.D.	Human
8	45	64	$2.1XL0_{-8}$	Human
9	133	64	$< 1x10_{-9}$	Poultry
10	109	64	$4.6x10_{-7}$	Poultry
11	57	32	N.D.	Human

(*1)in kilobases

(*2)minimal inhibitory concentration (mic) determined by agar dilution method.

(*3)frequencies are expressed as number of transconjugants per input donor cells.

ND=not determined

Table 18

ern gel containing plasmid DNA from each of the four classes and two subclasses of tetracycline determinants commonly found in the Enterobacteriaceae, as described by Mendez and co-workers (41). No homology was noted between the C. jejuni R-factor and any of the Enterobacteriaceae plasmids. Thus the plasmids of C. jejuni appear to be unique phenotypically and genetically from those seen in the Enterobacteriaceae.

H. Results of Serotyping

All C. jejuni isolates from food and case surveillance systems were forwarded to the Centers for Disease Control, Atlanta, Georgia, for serotyping. That work, performed under a separate contract between FDA and CDC, was performed by the Campylobacter Reference Laboratory, Division of Bacterial Diseases. Two serotyping systems, those of Lior (42) and Penner (43) were used to test all isolates. Serotyping results were made available for analysis with other data collected under the present contract.

In the present section, a summary of results of Lior serotyping of C. jejuni isolates from the food and human surveillance systems are presented. Of particular interest were the frequency of serotype distribution among various groups of C. jejuni isolates and correlations between serotype and antibiotic susceptibilities.

Many Lior serotypes were represented among 525 isolates from the present study that were tested. Most isolates

reacted with only one Lior antiserum, but 34 (6.5%) were reported as showing two Lior serotypes. Lior type 36 was the common serotype, accounting for 119 isolates (22.7%); type 4 was second in frequency, with 53 isolates (10.1%).

Table 19 shows the distribution of the most frequent Lior serotypes among isolates from processor products, retail poultry, and humans. Type 36 was most prevalent in all groups; other serotypes represented among the most frequent in all groups were serotyps 4,1, and 6. Of interest is the fact that there was complete homology among the 6 most frequent serotypes of retail poultry and humans (serotypes 1,2,4,6,9 and 36, Table 19).

Table 20 gives the frequency of tetracycline resistance in the six most prevalent Lior serotypes. Implicit in this correlation between serotype and tetracycline resistance is a similar correlation between carriage of the plasmid mediating tetracycline resistance and Lior serotype. This assumption is permitted by the documented correlation between tetracycline resistance and plasmid carriage, as reported in Results Section G.

There was considerable variation in the frequency of tetracycline resistance in various Lior serotypes (Table 20). In general, serotype 6 isolates had a lower frequency of tetracycline resistance than the others, while serotype 1 strains showed a relatively high frequency of tetracycline resistance. The rates of tetracycline resistance of Lior serotype 36, the most prevalent serotype, were similar among human and retail poultry iso-

Table 19

Most Frequent Lior Serotypes Among C. jejuni Isolates From Processor Products, Retail Poultry, and Humans

	Processor Products n=129		Retail Poultry n=165		Humans n=231	
Rank(*1)	Sero-type	%(*2)	Sero-type	%	Sero-type	%
1	36	(33.3%)	36	(23.0%)	36	(16.5%)
2	11	(18.6%)	4	(8.5%)	1	(12.6%)
3	4	(11.6%)	6	(7.3%)	4	(10.4%)
4	1	(3.9%)	1	(6.7%)	6	(9.1%)
5	6	(3.9%)	2	(6.7%)	9	(6.1%)
6	17	(3.9%)	9	(4.8%)	2	(4.8%)
7	28	(3.9%)				

(*1)In decreasing order of frequency.

(*2)Percent of all isolates represented within the given serotype.

Table 20

Frequency of Tetracycline Resistance(*1) Among
C. jejuni Isolates from the Six Most
Prevalent Lior Serotypes

Serotype	Tetracycline Resistance: # Resistant/# Tested (%)		
	Processor Products	Retail Poultry	Humans
1	2/5 (40%)	6/11 (54.5%)	11/29 (37.9%)
2	0/3 (0%)	4/11 (36.4%)	8/11 (72.7%)
4	1/15 (6.7%)	2/14 (14.3%)	8/24 (33.3%)
6	0/5 (0%)	1/12 (8.3%)	1/21 (4.8%)
9	0/1 (0%)	3/8 (37.5%)	4/14 (28.6%)
36	4/43 (9.3%)	11/38 (28.9%)	13/38 (34.0%)

(*1)Based on results of Kirby-Bauer susceptibility testing.

lates, but those rates (28.9% and 34.0%) were considerably greater than that (9.3%) of isolates from processor products (Table 20).

I. *Campylobacter jejuni* Case-Control Study

1. Response Rates.

Table 21 shows that roughly 97% of *C. jejuni* cases and 95% of *Salmonella* cases who met the study's inclusion criteria agreed to be interviewed. The response rate for controls, 61.6%, was considerably less than that for cases.

Laboratory test results for bacterial isolates sampled from, as well as all available demographic information available on the 7 eligible *C. jejuni* cases who refused participation, were utilized in all pertinent analyses. Accurate exposure information was missing for 2 cases who had difficulty pinpointing the onset of their symptoms although their illness began during the study period. Finally, for some of the tables in the analysis, an additional case was eliminated due to an illness reported in the 7 days prior to "onset", which was compatible with a *C. jejuni* prodrome suggesting the reported "onset" was unreliable.

Table 21. Case/Control Study: Response Rates.

		Cases	Controls	Salmonellas
A.	Total Selected	292	1203	105
B.	Ineligibles	67	193	19
C.	Lost		65	12
D.	MD Refusals		22	
E.	Refusals	7	328	4
F.	Excluded		58	
G.	Wrong family member interviewed*		11	
H.	Interviewed	218	526	72
	Response Rate for Confirmed Eligible Subjects $\frac{H}{H+E}$	$\frac{218}{225}$=96.9%	$\frac{526}{854}$=61.6%	$\frac{72}{76}$=94.7%

* These interviewees were eliminated from all analysis.

Among Salmonella cases, seven were unsure of when their illness began (although it was during the study period) and two were infected with C. jejuni as well as Salmonella and were included in the C. jejuni case groups. One additional Salmonella case was also infected with C. jejuni but was only included in the C. jejuni case group as the Salmonella was not one of the eligible serotypes at the time it was identified.

2. Validity Checks.

a. Telephone Validations

Roughly every 10th C. jejuni case or control subject was selected for validation phone calls, and 70 out of 81 eligible subjects were successfully contacted.

Two questions were asked of only 33 subjects: the first regarding health food consumption and the second, contact with animals during the week before onset/interview.

Overall, 88% of the validation responses were consistent with those given during the home interview even though the validation calls may have followed the interview by as much as 42 days.

All 70 subjects were asked about their years of education as well as symptoms in themselves and their contacts. 86% of the responses given the second time matched those given in the home interview regarding symptoms and years of education. Those that did change their response did so by only one symptom or year of education.

The 21 cases whose interviews were validated were asked again about when they first felt ill and well. On the average the 19 cases who could recall were within one day of their first response; although one case cited an onset that differed by 7 days from the one first given. A few cases differed from their home interview regarding a date of onset by 2-3 days. The average disagreement between both interviews for the 10 cases who were able to recall the date they first felt well was 0.2 days and the range of disagreement, 0-3 days.

b. Chart Check

Confirmation of responses was conducted for 31 subjects (roughly every 20th subject who entered the study). Interview responses were compared with GHC medical records by GHC Center for Health Studies personnel regarding onset of any symptoms, use of an antibiotic in the 7 days prior to their onset of symptoms/interview, number of well-care visits, and whether or not they were under a physician's care for chronic illness. For the cases, what antibiotic or antidiarrheal treatment was used for their C. jejuni infection and whether or not they were hospitalized was also checked.

There was 91% agreement overall between the medical records and interviews for the 8 questions reviewed for cases and the 3 questions reviewed for controls. Disagreements involved one date of onset, treatment for C. jejuni, well-care visits, and whether or not the subject was under a physician's care for a chronic illness. No disagreement was observed for hospitalization, illness, or antibiotic use in the 7 days prior to onset/interview.

3. Non-respondent Follow-up.

129 of 228 (56.6%) controls who originally refused participation in the case-control study were randomly selected and evaluated for eligibility for inclusion in the follow-up non-respondent interview (Table 22). Of those 129, 88 were determined to be eligible based on the criteria used in the main case-control study. Those 88 were solicited for phone interview and 77 (84.6%) agreed.

Table 22. Case/Control Study. Response Rates for Follow-up Controls Who Were Selected from Those Who Refused the Full Home Interview.

	Number of non-respondents
A. Total Refusals	228
B. Selected for follow-up	129
C. Ineligible	41
1. Terminated GHC after original selection	26
2. Lost to follow-up	10
3. Never contacted originally	1
4. Terminated GHC prior to selection	1
5. Non-English speaking	3
D. Agreed to participate	77
E. Refused to participate	11
F. Eligible (B-C)=	88
Response Rate (D/F)=	84.6%

4. Participating Control Subjects vs. Non-respondent GHC Enrollees

The eligible GHC Enrollees who declined participation in the main study but agreed to the non-respondent telephone interview were contrasted with the control subjects for a variety of exposures during May and June of 1984. (See Appendix C for complete non-respondent analysis).

As can be seen in Tables C-1 through C-19 in Appendix C, overall, the controls who participated in the main study were less likely to be single adults, more likely to be younger, white, female, better educated (when the analysis was restricted to subjects at least 30 years of age to reduce confounding by age), and living in a rural area than the non-respondent follow-up subjects.

All but the educational and racial differences (P=0.02 and 0.04, respectively) between the two groups could be explained by sampling variablity. The rural differnece was of borderline significance (P=0.06).

With regard to the contrasted exposures, the controls reported less participation in outdoor activities (even when the analysis was restricted to those controls interviewed in the summer months) than did the briefly interviewed non-respondent subjects (P=0.0009). Additionally, a greater proportion of controls than the phoned non-respondents reported drinking raw milk (P=0.02) whereas the reverse was true for chicken consumption (P=0.0001).

Surface water consumption was slightly more common amongst

non-respondents who were followed-up than amongst controls in general or controls interviewed in the summer months.

The mean age of members of control household was slightly older than that of the briefly interviewed non-respondent subjects. The household of both groups did not differ with regard to sex or constituent relationships.

Reporting of animal contacts by both groups was roughly equivalent. When the subject was a child, mothers were more likely to be interviewed for the main study, whereas fathers participated more often in the phone interviews (P=0.00005).

5. Comparability of Cases and Controls

No significant difference was noted between cases and controls with regard to utilization of GHC well care visits.

6. Case/Control Misclassification

25 controls reported a mild diarrheal illness in the week prior to interview. Four of the 25 were cultured and were negative for enteric pathogens. The responses of these 25 controls for the "causal exposure" variables were analyzed separately from the controls who were not diarrheic. There was no difference between the two groups, therefore, the 25 controls with diarrheal illness were included in the results.

Because C. jejuni infection is rare in asymptomatic individuals in the U.S. (10), the chances of interviewing a control who was infected with C. jejuni were slim. Indeed, all 34 well control subjects who were randomly selected for culture had stools/rectal swabs that were negative for enteric pathogens.

7. Risk Factor Analysis

Exposures were classified into eight general categories: demographic factors, geographic location, travel-related, food-related, water-related, human contacts, animal-related, and miscellaneous. Results of this risk factor analysis will be presented in the following eight sections lettered a-h.

a. Demographic factors.

Two determinants of socio-economic status were analyzed. The first, a scaled measurment of socio-economic status as set forth by Steven and Featherman (44), the MSE12 Score, differed little between cases and controls. This method of determining social class is based on a national survey of the prestige, income, and educational attainment associated with the specific occupations as listed in the 1980 census.

The occupations used in this study to calculate the MSE12 were those of the heads of the index household (i.e., the index subject, spouses, unmarried partners, or parents). The highest MSE12 score in the household was the one used. The parents' occupations were used in this determination only if the index was still living at home and not yet graduated from high school.

Table 23. Relative Risk Associated with Socio-economic Status as Determined from the MSE12 Score.

MSE12 Score	Case	Control	RR	(95%CI)
0-39	54	132	1.0	
40-49	34	86	1.0	(0.6-1.6)
50-59	23	78	0.7	(0.4-1.3)
60-69	16	54	0.7	(0.4-1.4)
70-79	53	100	1.3	(0.8-2.1)
80-89	28	64	1.1	(0.6-1.9)
Unknown	17	12		
Total	225	526		

1)The mid-point for each range of MSE12 Scores was used to calculate trend.
2)The extension chi for trend with 1 degree of freedom=0.61, P=0.54

The second social class determinant used was education. The average number of years of education completed by the heads of the index household did not differ between case and control households. As with the MSE12 score, the parent's education was used only if the index case was under 20 years and still living at home.

Table 24. Relative Risk Associated with the Average Years of Education for the Heads of the Index Household.

Exposure	Case	Control	RR	(95%CI)
Education up to 11 years	10	14	1.0	
High school grad	27	70	0.5	(0.2-1.4)
Trade school	15	46	0.5	(0.2-1.2)
Some college	49	125	0.5	(0.2-1.3)
College grad	60	144	0.6	(0.2-1.4)
Post college	51	97	0.7	(0.3-1.8)
Unknown	13	30		
Total	225	526		

1)Trend was calculated using 10, 12, 13, 14, 16, and 21 as scores for each increasing level of education.
2)The extension chi for trend with 1 degree of freedom=1.0, P=0.32.

In addition, cases and controls did not differ significantly with respect to race.

Table 25. Relative Risk Associated with the Index Subject's Race.

Race	Case	Control	RR	(95%CI)
White	201	476	1.0	
Black	3	12	0.6	(0.2-2.1)
Asian	8	15	1.3	(0.5-3.0)
Other races	6	18	0.8	(0.3-2.0)
Unknown	7	5		
Total	225	526		

The overall chi square statistic with 3 degrees of freedom=1.2, P=0.75

Among the occupations categorized in the 1980 U.S. Census (Alphabetic and Classified Indexes of Industries and Occupations, 1980 Census of Population, U.S. Deptartment of Commerce, Bureau of Census) in which the members of the index households were employed, 25 were reported by the members of at least four case households. Those occupations were examined for any association with C. jejuni infection. Involvement by the index subject in two occupations, that of housewife or physician, was reported differentially by cases and controls (RR=2.3, 95% CI=1.2-4.6 and RR$\geq$2.0, respectively). The latter involved only two cases who were physicians.

However, when spouses, unmarried partners, or parents were included (i.e., the heads of the household); cases were more likely than controls to have in their households individuals employed as physicians (RR=6.6, 95% CI=2.1-21.2), or engineers (RR=3.3, 95% CI=1.5-7.7).

Persons reporting unknown occupations or employment status for any, but not all, household members were included in the results of the following table in the reference or unexposed category.

Table 26. Relative Risks Associated with Specific Occupation in Which the Heads of the Index Household Were Employed in the 7 Days before the Onset/Interview.

Occupation	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Housewife	62	150	156	376	1.0(0.7-1.4)	.98
Manager	16	46	202	480	0.8(0.5-1.5)	.53
Accountant	7	18	211	508	0.9(0.4-2.3)	.89
Electric Engineer	6	12	212	514	1.2(0.4-3.3)	.71
Engineer	12	9	206	517	3.3(1.5-7.7)	.01
Physician	8	3	210	523	6.6(2.1-21.3)	.01
Nurse	11	32	207	494	0.8(0.4-1.7)	.58
Nurse's aid	4	6	214	520	1.6(0.5-5.7)	.45
Elementary school teacher	6	22	212	504	0.6(0.3-1.6)	.35
Secondary school teacher	13	15	205	511	2.2(1.0-4.5)	.04
Other teachers or instructors	11	17	207	509	1.6(0.7-3.4)	.24
Social worker	6	15	212	511	1.0(0.4-2.5)	.94
Religious worker	5	20	213	506	0.6(0.2-1.6)	.30
Lawyers	5	16	213	510	0.7(0.3-2.1)	.58
Musician	4	3	214	523	3.3(0.8-13.5)	.24
Technician	4	5	214	521	2.0(0.5-7.2)	.50
Supervisors	6	13	212	513	1.1(0.4-3.0)	.82
Sales representative	4	2	214	524	4.9(1.0-22.9)	.12
Secretary	8	21	210	505	0.9(0.4-2.1)	.84
Bookkeeper	6	12	212	514	1.2(0.4-3.3)	.71
General office clerk	5	12	213	514	1.0(0.4-2.9)	.99

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Occupation	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Childcare worker	4	13	214	513	0.7(0.2-2.3)	.60
Carpenter	4	5	214	521	1.9(0.5-7.2)	.50
Electrician	4	7	214	519	1.4(0.4-4.8)	.60
Bus driver	4	5	214	521	2.0(0.5-7.2)	.50
Janitor	4	12	214	514	0.8(0.3-2.5)	.71

1)Information was unknown for 7 cases.
2)The probability value from Fisher's Exact Test or the chi-square with 1 degree of freedom.

Among five possible types of marital relationships that were reported by subjects, two were more often reported by cases than by controls: being widowed (RR=3.7, 95% CI=1.1-12.2) or living-as-married (RR=3.1, 95% CI=1.6-6.0). Marital status refers to the parents or the guardian of the index if the subject was still living at home and not yet graduated from high school.

Table 27. Relative Risk Associated with Marital Status

Marital Status	Case	Control	RR	(95%CI)	P
Married	154	400	1.0		
Never married	26	63	1.1	(0.7-1.8)	
Separated	13	41	0.8	(0.4-1.6)	
Widow	6	4	3.9	(1.2-12.8)	
Living-as-married	18	15	3.1	(1.6-6.2)	0.003[1]
Widow	6	4	3.7	(1.1-12.2)	0.03[2]
Not widow	211	519	1.0		
Living-as-married	18	15	3.1	(1.6-6.0)	0.001[2]
Not living-as-married	199	508	1.0		
Unknown	8	3			
Total	225	526			

1)The probability value from the chi-square statistic with 4 degrees of freedom.
2)The probability value from the chi-square statistic with 1 degree of freedom

When the relationship of the index to other household members (see Table 29) or the index household composition (see Table 28) were examined for clues as to whom and what types of households are at greatest risk of C. jejuni infection, again only households which contained unmarried sexual partners were were observed more often among cases than among controls.

Table 28. Relative Risk Associated with the Household Type as Classified by Its Composition in the 7 Days Before Onset/Interview.

Household Type	Case	Control	RR	(95%CI)
Solo index	11	29	1.0	
House w/infant	31	111	0.7	(0.3-1.6)
House w/preschoolers	43	139	0.8	(0.4-1.8)
House w/5-9 yr olds	22	75	0.7	(0.3-1.8)
House w/10-19 yr olds	30	63	1.3	(0.6-2.9)
Married Couples	60	76	2.1	(1.0-4.5)
Other adult relatives living together	10	14	1.9	(0.6-5.5)
Unrelated adults living together	10	19	1.4	(0.5-3.9)
Unknown	8	0		
Total	225	526		

The overall chi-square statistic with 7 degrees of freedom=25.8, P=0.0006.

Table 29. Relative Risk Associated with the Position of the Index in the Usual Household (Excludes Visitors).

Position	Case	Control	RR	(95%CI)
Solo index	15	30	1.0	
Spouse (can also be parent)	99	214	0.9	(0.5-1.8)
Single parent	6	17	0.7	(0.2-2.2)
Child 18 or under	61	218	0.6	(0.3-1.1)
Unmarried partner (can also be parent)	19	11	3.5	(1.3-9.0)
Roommate	9	19	1.0	(0.3-2.6)
Other relatives	9	17	1.1	(0.4-3.0)
Unknown	7	0		
Total	225	526		

The overall chi-square statistic with 6 degrees of freedom=26.0, P=0.0002.

As can be seen in Table 30, the size of the household differed little between the cases and control subjects.

Table 30. Relative Risk Associated with Usual Household Size.

Household Size	Case	Control	RR	(95%CI)
Single	15	30	1.0	
Couple	70	99	1.4	(0.7-2.8)
Trio	48	141	0.7	(0.3-1.4)
Four	47	170	0.6	(0.3-1.1)
Five to Twelve	38	86	0.9	(0.4-1.8)
Unknown	7	0		
Total	225	526		

1)The mid-point of the range of each category of household size was used to test for trend (1.0, 2.0, 3.0, 4.0, 8.5).
2)The extension chi with 1 degree of freedom=1.1, two-tail P=0.32.

b. Geographic location.

Three methods of categorizing the geographic location of the index's primary residence were analyzed: zip code, census tract, and county location codes. Very little difference was noted between cases and controls with regard to residential zip codes or census tracts.

The following table results from an analysis of geographic residential zones. Little difference in terms of geographic area of residence was observed.

Table 31. Relative Risk Associated with the Location of Index Household.

Location	Case	Control	RR	(95%CI)
SW Snohomish County	21	44	1.1	(0.7-1.9)
NW King County	71	145	1.2	(0.9-1.7)
NE King County (Bothell, Woodinville, Kirkland & Carnation areas)	19	50	0.9	(0.5-1.5)
W King County (West and South Seattle areas)	34	79	1.0	(0.7-1.6)
Downtown Seattle	15	18	2.0	(1.0-4.0)
Central East King County (Mercer Island, Bellevue and Medina areas)	23	45	1.2	(0.7-2.1)
SE King County (Renton and Coalfield areas)	11	26	1.0	(0.5-2.0)
SW King County (Burien, Kent, Des Moines, Vashon, and Federal Way areas)	22	80	0.6	(0.4-1.0)
South South East King County (Maple Valley, Black Diamond and Enumclaw areas)	4	26	0.3	(0.1-1.0)
Central Central East King County (Issaquah, Lake Sammamish, North Bend and Snoqualmie areas)	5	13	0.9	(0.3-2.5)
Total	225	526		

The overall chi-square statistic with 9 degrees of freedom=12.9, P=0.17

The distribution of population density for the subject's area of residence, based on 1980 residential census tract information, revealed that proportionally more controls participated from the most and the least dense areas of population. These differences between cases and controls were not statistically significant and most likely reflect the greater propensity for GHC enrollees from more rural zip codes to participate as control subjects. Controlling for population density using the 5 categories in Table 32 below did not alter the risk estimate for any of the suspected causal exposures.

Table 32. Relative Risk Associated with the Population Density of the Census Tract in Which the Index Resides.

Population Per Square Mile	Case	Control	RR	(95%CI)
Less than 1000	18	70	1.0	
1000-4999	105	255	1.6	(0.9-2.8)
5000-9999	88	170	2.0	(1.1-3.6)
10000-14999	13	23	2.0	(0.9-4.8)
15000-39999	1	8	0.5	(0.1-4.0)
Total	225	526		

1)The mid-point of the range for each category of density above was used to test for trend.
2)The extension chi for trend with 2 degrees of freedom=1.0, P=0.32.

c. Travel-related exposures.

Little increased risk of C. jejuni infection was observed in those who traveled at least 30 miles (excludes regular commuting) within the U.S. or other developed nations such as Canada, Europe, or Scandinavia when compared to non-travelers. However, travel to less developed nations such as Mexico, India, and China was strongly associated with the risk of C. jejuni infection (RR=36.9, 95% CI=10.2-133.6).

Table 33. Relative Risk Associated with the General Categories of Travel Destination.

Exposure	Case	Control	RR	(95%CI)
No travel	127	360	1.0	
Within the U.S.	73	155	1.3	(1.0-1.9)
To a developed foreign country	1	9	0.3	(0.0-2.3)
To an undeveloped foreign country	13	1	36.9	(10.2-133.6)
Unknown	11	1		
Total	225	526		

For calculation of the overall chi-square statistic, all travel within the U.S. and to other developed nations were grouped. The overall chi-square statistic with 2 degrees of freedom=30.3, P=0.0000002.

For description purposes, all destinations to which at least one case traveled are included in the following table. Although travel to Mexico, China, and India was only reported by cases, travel to Canada and other developed nations was reported slightly more often by controls.

In the week prior to onset or interview, several Washington counties were more likely to have been visited by cases than by controls: Island County (RR=5.7, 95%CI=1.9-16.9), Okanogan (RR=8.5, 95%CI=1.3-57.1), and Snohomish (RR=2.2, 95%CI=1.0-4.5).

In the table that follows, each of the categories were contrasted with no travel. The destinations are not mutually exclusive, thus an individual could have traveled to more than one destination.

Table 34. Relative Risk Associated with Specific Travel Destinations.

Travel Destination	Case	Control	RR	(95%CI)	P
King County≥30 miles from home	9	48	0.5	(0.3-1.1)	.09
Snohomish County	13	17	2.2	(1.0-4.5)	.04
Kitsap County	4	7	1.6	(0.5-5.6)	.44
Island County	8	4	5.7	(1.9-16.9)	.002
Whatcom County	2	4	1.4	(0.3-7.8)	.98
Skagit County	2	5	1.1	(0.2-5.9)	1.00
Jefferson County	3	2	4.3	(0.8-22.4)	.24
Grays Harbor County	1	4	0.7	(0.1-6.4)	1.00
San Juan County	3	3	2.8	(0.6-13.3)	.38
Okanogan County	3	1	8.5	(1.3-57.1)	.12

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Travel Destination	Case	Control	RR	(95%CI)	P
Mason County	2	3	1.9	(0.3-11.2)	.78
Pierce County	8	28	0.8	(0.4-1.8)	.62
Chelan County	1	8	0.4	(0.1-2.6)	.58
Kittitas County	4	3	3.8	(0.9-15.5)	.16
Yakima County	1	4	0.7	(0.1-6.4)	1.00
Benton County	2	2	2.8	(0.4-18.8)	.28
Spokane County	2	1	5.7	(0.7-48.2)	1.00
Texas	1	1	2.8	(0.2-40.7)	.92
Oahu	2	0	Inf	(---)	.14
Oregon	7	9	2.2	(0.8-5.9)	.11
Idaho	1	0	Inf	(---)	.52
Alaska	1	0	Inf	(---)	.52
California	2	4	1.4	(0.3-7.8)	.98
Utah	1	0	Inf	(---)	.52
Colorado	2	1	5.7	(0.7-48.2)	.34
Minnesota	1	0	Inf	(---)	.52
Canada	2	6	1.0	(0.2-4.8)	1.00
Mexico	11	0	Inf	(---)	.00000
India	1	0	Inf	(---)	.52
China	2	0	Inf	(---)	.14
Did not travel at all	127	360	1.0		
Unknown	10	1			

The probability value from Fisher's Exact Test or the chi-square statistic with 1 degree of freedom.

Waters drunk in specific locations by at least three cases were screened as potential sources of infections with C. jejuni. As few traveled to these locations and did not drink, it is not possible to determine with any degree of certainty whether or not drinking water in these location was implicated.

Table 35. The Relative Risk Associated with Drinking Water Location.

Location	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Snohomish County (outside study area)	3	6	196	506	1.3(0.3-5.2)	0.98
Island County	8	1	191	511	21.4(4.9-92.8)	0.0004
San Juan County	3	1	196	511	7.8(1.1-53.4)	0.14
Mexico	11	0	190	512	Inf(≥25754)	0.00000

Information was unknown for 26 cases and 14 controls.

The probability value from the Fisher's Exact Test.

Another travel-related category of exposure, that of outdoor activities in remote areas including backpacking, hiking, camping, trail riding, and skiing, picnicking, mountaineering, etc. was also examined for its potential role in the epidemiology of human C. jejuni infection. Cases were more likely than controls to report such activities in remote areas (RR=1.8, 95% CI=1.2-2.6).

The following specific activities were not associated with C. jejuni infection: horseback riding, hiking, car camping, and playing in sand.

d. Food-related exposures

Subjects were asked about whether or not they had eaten a wide variety of specific food items in the week prior to onset/interview. Unless indicated on the questionnaire or written in the table below, infants did not eat these foods and were excluded from these analyses. In all cases, the unexposed categories for each item include those subjects who reported that they did not eat the particular food.

Several foods were implicated as potential sources of human C. jejuni infection. A quadrupling of the point estimate of the relative risk was observed in those who drank raw milk when compared to those who didn't (RR=4.6, 95%CI=2.1-10.4). This effect was strongest in the colder months of November thru March (RR=11.7, 95%CI=3.6-38.3) than in the summer months (RR=3.4, 95%CI=1.2-9.8). All of the exposed were under age 40.

Chicken consumption, especially that of raw or rare chicken, was also associated with a significant increase in risk (cooked chicken, RR=2.3, 95%CI=1.5-3.5; rare chicken, RR=7.6, 95%CI=2.1-27.6).

Cases were three times as likely as controls to have consumed Cornish game hen or other domestic fowl aside from chicken and turkey in the week prior to onset/interview (RR=3.3, 95% CI=1.1-9.8). Those who consumed processed turkey sandwich meats experienced a 70% increase in risk when compared those who did not (RR=1.7, 95% CI=1.0-2.9).

The consumption of raw or rare fish (e.g. sushi) was associated with an increase in the risk of C. jejuni infection when compared to the risk in those who did not eat raw or rare fish (RR=4.0, 95%CI=1.1-14.5).

One last food, mushrooms, was reported to have been eaten more often by cases than by controls in the week prior to onset/interview (RR=1.5, 95%CI=1.1-2.1).

Table 36. Relative Risk Associated with Specific Foods Eaten in the Seven Days Prior to Onset/Interview.

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Dairy products:						
Pasteurized milk	183	424	25	53	0.9(0.6-1.5)	.73
Whole milk	76	158	130	315	1.2(0.8-1.6)	.38
Chocolate milk	5	29	203	447	0.4(0.2-1.0)	.04
Skim milk	8	30	199	446	0.6(0.3-1.3)	.20
Low fat milk	4	23	203	453	0.4(0.1-1.1)	.07
2% or acidophilis milk	102	247	105	227	0.9(0.6-1.2)	.50
Cocoa	19	75	187	397	0.5(0.3-0.9)	.02
Shake	27	52	178	420	1.2(0.8-2.0)	.42
Milk beverage	46	129	162	347	0.8(0.5-1.1)	.17
Yogurt	64	133	143	342	1.2(0.8-1.6)	.44
Ice cream	123	297	76	174	1.0(0.7-1.3)	.76
Ice milk	7	9	198	462	1.8(0.7-4.9)	.24
Sherbert	5	21	200	449	0.5(0.2-1.4)	.21
Pudding	15	43	189	428	0.8(0.4-1.5)	.45
Milk dessert	138	340	65	133	0.8(0.6-1.2)	.31
Half'n Half	17	48	187	425	0.8(0.5-1.4)	.46
Sourcream	56	98	148	372	1.4(1.0-2.1)	.06
Whipcream	26	70	176	402	0.9(0.5-1.4)	.51
Creams	87	192	117	279	1.1(0.8-1.5)	.65
Creamy dips/dressings	104	228	98	247	1.2(0.8-1.6)	.41
Creamed soups	49	137	156	338	0.8(0.5-1.1)	.19
Raw goat milk[2]	1	2	195	515	1.3(0.1-14.6)	1.00
Raw milk[3]	14	8	195	515	4.6(2.1-10.4)	.0002

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Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Cheeses:						
Any Soft	87	209	119	267	0.9(0.7-1.3)	.69
Cottage	53	118	149	354	1.1(0.7-1.6)	.74
Farmer's	2	3	201	469	1.6(0.3-9.3)	.94
Ricotta	7	8	196	464	2.1(0.8-5.7)	.16
Cream	39	80	163	392	1.2(0.8-1.8)	.46
Any hard cheeses	179	433	28	43	0.6(0.4-1.1)	.08
Cheddar/Colby/Long Horn	143	356	60	115	0.8(0.5-1.1)	.16
Havarti	7	18	199	455	0.9(0.4-2.2)	.80
Parmesan	48	101	155	372	0.1(0.8-1.7)	.51
Monterey Jack	21	73	185	400	0.6(0.4-1.0)	.07
Swiss	39	68	168	404	1.4(0.9-2.1)	.14
Gouda	3	7	204	465	1.0(0.3-3.8)	.97
Edam	2	7	205	466	0.7(0.1-3.1)	.90
Mozzarella	42	131	165	341	0.7(0.5-1.0)	.04
Blue	6	31	201	442	0.4(0.2-1.0)	.05
Eggs:						
Cooked	170	407	37	70	0.8(0.5-1.2)	.29
Raw	22	53	184	422	1.0(0.6-1.6)	.85

continued--

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Mixes, tofu and desserts:						
Pancake mix	62	150	138	313	0.9(0.7-1.3)	.72
Muffin, bread or cake mix	21	71	183	384	0.6(0.4-1.0)	.07
Tofu	12	24	198	447	1.1(0.6-2.3)	.74
Glazed desserts	105	278	98	197	0.8(0.6-1.1)	.10
Cream-filled dessert	19	65	189	409	0.6(0.4-1.1)	.09
Unprocessed pork:						
Any pork	82	188	124	286	1.0(0.7-1.4)	.97
Uncured sausage	11	38	189	416	0.6(0.3-1.3)	.20
Cuts of pork	69	143	131	313	1.2(0.8-1.6)	.43
Unprocessed beef:						
Any beef	183	427	23	48	0.9(0.5-1.5)	.68
Beef organ	5	13	203	462	0.9(0.3-2.5)	.80
Unprocessed poultry:						
Any turkey	32	88	174	385	0.8(0.5-1.3)	.34
Any chicken	171	325	33	151	2.4(1.6-3.6)	.00003
Cooked chicken	162	319	33	151	2.3(1.5-3.5)	.00007
Rare or raw chicken	5	3	33	151	7.6(2.1-27.6)	.02
Domestic fowl	7	5	202	473	3.3(1.1-9.8)	.03

continued--

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Unprocessed seafood:						
Any fish	84	163	123	310	1.3(0.9-1.8)	.13
Rare or raw fish[3]	6	5	200	469	4.0(1.1-14.5)	.04
Any shellfish	68	116	141	360	1.5(1.1-2.1)	.03
Rare or raw shellfish	3	5	203	469	1.4(0.3-5.8)	.92
Unprocessed game:						
Game	6	14	204	464	1.0(0.4-2.6)	.96
Processed pork:						
Any pork	154	361	55	115	0.9(0.6-1.3)	.55
Pork sausage	58	145	152	326	0.9(0.6-1.2)	.40
Cured ham	50	147	160	325	0.7(0.5-1.0)	.05
Pork sandwich meat	36	81	175	392	1.0(0.7-1.5)	.98
Pork hot dog	37	86	173	385	1.0(0.6-1.5)	.84
Bacon	79	169	131	301	1.1(0.8-1.5)	.68
Pork'n beans	4	10	207	462	0.9(0.3-2.9)	.85
Processed beef:						
Any beef	117	292	87	182	0.8(0.6-1.2)	.30
Beef salami	31	86	176	381	0.8(0.5-1.2)	.28
Beef sandwich meat	57	122	152	345	1.1(0.7-1.5)	.75
Beef jerky	7	7	202	460	2.3(0.8-6.4)	.12
Beef hot dogs	57	142	147	327	0.9(0.6-1.3)	.54
Corned beef	7	22	202	445	0.7(0.3-1.7)	.42
Beef TV dinner	7	16	202	450	1.0(0.4-2.4)	.96
Canned beef soup	3	17	206	450	0.4(0.1-1.3)	.12

continued--

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Processed poultry:						
Any turkey	48	94	154	382	1.3(0.9-1.9)	.24
Turkey roll	14	29	193	440	1.1(0.6-2.1)	.78
Turkey sandwich meat	27	38	177	431	1.7(1.0-2.9)	.04
Turkey hot dog	10	15	196	454	1.5(0.7-3.5)	.29
Turkey TV dinner	1	10	206	459	0.2(0.0-1.5)	.12
Chicken	24	97	179	377	0.5(0.3-0.8)	.007
Chicken sandwich meat	6	11	200	460	1.3(0.5-3.4)	.66
Chicken dog	3	16	203	455	0.4(0.1-1.4)	.16
Chicken TV dinner	9	41	195	429	0.5(0.2-1.0)	.05
Canned chicken soup	5	24	202	446	0.5(0.2-1.2)	.11
Processed lamb or mutton:						
Any lamb or mutton	12	25	195	450	1.1(0.6-2.3)	.78
Processed fish:						
Any fish	95	229	111	246	0.9(0.7-1.3)	.62
Canned fish	77	189	129	284	0.9(0.6-1.3)	.53
Smoked fish	9	17	201	458	1.2(0.5-2.8)	.66
Fish TV dinner	10	35	198	440	0.6(0.3-1.3)	.21
Canned fish soup	7	10	203	465	1.6(0.6-4.2)	.34
Processed shellfish	23	51	185	422	1.0(0.6-1.7)	.92

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Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Vegetables:						
Leafy green salad vegetables	193	428	17	49	1.3(0.7-2.3)	.37
Cucumbers, zucchini or carrots	179	392	30	84	1.3(0.8-2.0)	.29
Leeks or onions	163	351	46	118	1.2(0.8-1.8)	.38
Tubers	166	389	43	86	0.9(0.6-1.3)	.45
Brussel sprouts, broccoli or cauliflower	96	219	112	255	1.0(0.7-1.4)	.99
Beans	45	95	162	382	1.1(0.8-1.7)	.59
Mushrooms	108	206	94	269	1.5(1.1-2.1)	.02
Health or organically-grown foods	46	95	152	372	1.2(0.8-1.8)	.40
Unpeeled produce	165	402	40	74	0.8(0.5-1.2)	.20
New foods never before eaten	60	136	146	337	1.0(0.7-1.5)	.92

1The probability value from Fisher's Exact Test or the chi-square statistic with 1 degree of freedom
2 Raw cow's milk drinkers were excluded from this analysis.
3 Two infants were included in this analysis.

Note. The subjects who were not queried (i.e., infants) or who did not know whether or not they had eaten a particular item are not included in the table.

Information was unknown for 14-29 cases and 3-71 controls.

Parents of index subjects less than one year of age were queried about a variety of infant foods and formulas which their child might have eaten in the week before onset/interview. Two items were differentially consumed by case and control infants: commercially prepared baby foods which contained meat (RR=4.9, 95% CI=1.4-17.5), and those which contained vegetables (RR=3.9, 95% CI=1.1-14.4), As Table 37 illustrates, the number of infants exposed to those items was small, thus the risk estimates were extremely sensitive to any changes in the numbers in the various exposure categories. This effectively prevented adjustment for other factors.

In addition, infants who shared table food with the rest of the family experienced a greater risk of C. jejuni infection than those who did not (RR=3.9, 95% CI=1.1-13.2).

The following table includes foods fed to the subjects who were under one year of age on the date of onset/interview. Only exposures for which there were sufficient numbers to provide expected values for each cell of 75 75 were included. Occasionally, a toddler who was still eating baby foods or formula was included in these responses.

Table 37. Relative Risk Associated with Infant Foods and Formulas.

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Breast fed	7	49	5	27	0.8(0.2-2.7)	.68
2% milk	3	9	9	66	2.4(0.6-10.5)	.23
Commercial formula	6	43	6	33	0.8(0.2-2.6)	.67
Commercial meat baby food	5	11	6	65	4.9(1.4-17.5)	.01
Commercial vegetable baby food	6	21	4	55	3.9(1.1-14.4)	.04
Vitamin supplement	1	12	11	64	0.5(0.1-4.0)	.50
Fruit baby food	3	11	4	47	3.2(0.7-15.6)	.15
Was infant fed table food in 7 before	8	26	4	50	3.9(1.1-13.2)	.03

The parent/guardian of 12 case and 77 control subjects responded to the above questions. Variable totals are due to unknown responses for some of the questions.

The probability value from the chi-square statistic with 1 degree of freedom.

The type of retail outlet where the food eaten was purchased was analyzed. Purchasing foods from a delicatessen was associated with a 100% increase in risk of C. jejuni infection in those who did, when compared to the risk in those who did not buy their food from such retail outlets (RR=2.0, 95% CI=1.2-3.4).

Meals eaten away from home either at social gatherings or while in restaurants were equally reported by cases and controls.

Table 38. The Relative Risk Associated with Eating Food from Specific Types of Retail Outlets

Type of Market, Store or Counter	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Supermarket	196	498	13	20	0.6(0.3-1.2)	.17
Grocery	50	93	156	394	1.4(0.9-2.0)	.12
Deli	27	34	179	453	2.0(1.2-3.4)	.009
Fast food	35	103	174	413	0.8(0.5-1.2)	.32
Health food	21	50	192	465	1.0(0.6-1.7)	.95
Open market	30	51	179	465	1.5(1.0-2.5)	.08
Roadside stand	12	40	199	476	0.7(0.4-1.4)	.33

Information was unknown for between 12-19 cases and 7-10 controls.

The probability value from the chi-square statistic with 1 degree of freedom.

An attempt was made to ascertain the potential crosscontamination during food preparation which might have occurred in the index household. This was done by asking about methods of cleaning the surfaces on which meat, fish, and poultry were prepared.

An eight-point scale, the "Cutting Board Scale," was used, based on practices such as use of soap and hot water, frequency of cleaning, and whether or not separate suraces were used for foods that required cooking and those that did not.

Controls scored higher (indicating safer practices) on the average than did cases with regard to the "Cutting Board Scale." As can be seen below in Table 39, a statistically significant linear trend was observed with an increasing risk estimate associated with decreasing scores on the "Cutting Board Scale."

Only a subset of the subjects was asked about cutting board practices in the week before onset/interview. The remainder were asked about "usual" practices relating to food preparation surfaces. The results for the analysis of usual practices were similar to those for practices in the "week prior" (P Trend= 0.04). For the 6 subjects who were asked both questions, the responses both were identical.

Table 39. Relative Risk Associated with Practices Relating to Food Preparation Surfaces--Cutting Board Scale in the 7 Days Before Onset/Interview.

Score	No. Exposed Cases	Controls	RR	95% CI
2-4 points	15	21	2.7	(1.0-4.4)
5 points	18	36	1.5	(0.7-2.9)
6 points	29	59	1.4	(0.8-2.5)
7-10 points	40	117	1.0	
Unknown	123	293		
Total	225	526		

1)The mid-point of the range for each category above was used to test for trend.
2)The extension chi for trend with 1 degree of freedom=-2.1, P=0.04

e. Water-related exposures.

A variety of exposures related to drinking water and water used for recreational purposes were examined as potential risk factors for C. jejuni infection. The residential water supply during the week before onset/interview was determined from Water District and State Health Department records using the subject's address to verify the water district reported during the interview.

Non-metropolitan water supplies were reported roughly twice as often by controls as by cases. This meant that those factors which describe such supplies (i.e., partial or no chlorination, well and/or spring sources, and less than 100 service connections were found to supply proportionately more control than case homes.

Table 40. The Relative Risk Associated with Chlorination of Home Water Supply.

Exposure	Case	Control	RR	(95%CI)
Variable, partial or no chlorination	14	64	0.5	(0.3-0.9)
Full chlorination	203	457	1.0	
Unknown	8	5		
Total	225	526		

The overall chi-square statistic with 1 degree of freedom=5.5, P=0.02.

Table 41. The Relative Risk Associated with the Source of the Home Water Supply.

Source of Water	Case	Control	RR	(95%CI)
Major reservoir or river	193	428	1.00	
Well, spring or both	25	97	0.6	(0.4-0.9)
Unknown	7	1		
Total	225	526		

The overall chi-square statistic with 1 degree of freedom=5.5, P=0.02.

Several types of non-home drinking water exposures were reported more often by cases than controls. The non-home drinking waters explored for their potential role in C. jejuni infection included: well, surface, and bottled water.

Adjustment for travel to an undeveloped foreign nation did not alter the risk estimates associated with the consumption of the various types of water with the exception of bottled water. The effect of increased risk associated with the consumption of well or surface water was restricted to those who remained in the U.S.(RR=1.9,95%CI=1.2-3.1). Although bottled water was consumed by seven of those who traveled to undeveloped foreign nations, it was not possible to determine if it was involved as a source of C. jejuni infection.

Table 42. The Risk Associated with Drinking Specific Types of Non-Home Waters as Compared to Not Drinking Those Waters

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Drank well water	20	36	172	472	1.5(0.9-2.7)	0.15
Drank lake or pond water	8	8	203	515	2.5(1.0-6.6)	0.06
Drank river creek or stream water	9	9	203	514	2.5(1.0-6.3)	0.04
Drank bottled water[2]	21	28	189	498	2.0(1.0-3.5)	0.002

Information for the above exposures was unknown for 13-33 cases and 0-13 control subjects.

1)The probability value from the chi-square statistic with 1 degree of freedom.
2)Adjusted for travel to an undeveloped foreign nation+.

Swimming, bathing or playing in the salt or fresh water was not associated with C. jejuni infection.

Table 43. The Relative Risk Associated with Water Recreation (Swimming, Skiing, etc.) in Specific Waters.

Exposure	Case	Control	RR	(95%CI)	P
Ocean[2]	10	7	2.7	(1.0-7.3)	.10
Sound[2]	10	19	1.2	(0.6-2.7)	1.00
No salt swim	178	483	1.00		
Unknown	27	17			
Total	225	526			
Lake, Pond	23	37	1.6	(1.0-2.8)	.09
River, Creek	8	9	2.3	(0.9-5.9)	.08
No fresh water	184	476			
Unknown	10	4			
Total	225	526			

1)The probability value from the chi-square statistic with 1 degree of freedom.
2)Adjusted for drinking surface, well, or bottled water while ≥30 miles from home.

Four times the proportion of cases as compared to contols claimed to have showered in untreated water (RR=4.3, 95% CI=1.2-16.2).

Table 44. The Relative Risk Associated with Showering in Untreated Water.

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)
Showered with untreated water[2]	14	3	200	520	4.3(1.2-16.2)

Information for both travel and showering was unknown for 11 cases and 3 controls.

1)The Mantel-Haenszel chi with 1 degree of freedom=2.2, P=0.003.
2)The analysis was controlled for travel to an undeveloped foreign nation±.

The remaining water activities which were examined for their potential role in C. jejuni infection were equally reported by cases and controls. They included use of: hot tubs, saunas, and jacuzzis.

Table 45. The Relative Risk Associated with Specific Types of Recreational Tubs.

Exposure	Case	Control	RR	(95%CI)	P
Sauna	2	9	0.5	(0.1-2.5)	.42
Jacuzzi	7	9	1.9	(0.7-5.0)	.21
Hot tub	3	12	0.6	(0.2-2.1)	.43
All tubs	12	30	1.0	(0.5-1.9)	.92
No tubs	204	493	1.0		
Unknown	9	3			
Total	225	526			

The probability value from the chi-square statistic with 1 degree of freedom.

f. Household contacts.

As can be seen in Table 46, cases were more likely than controls to report illness in their household contacts either before, on, or after the date of onset/interview. In order to evaluate the degree of transmission to others occurring after the case's date of onset, it was necessary to query controls about illness occurring in contacts in a comparable time period. Thus, controls were asked about illness in contacts occurring in the second and third weeks prior to interview. Calendars were used during interviews to help pinpoint exact time frames for exposures. From here on, that reference time frame will be referred to as the "time after" the index date.

As the incubation period for C. jejuni infection ranges from 4 hours to 7 days (10, 11), co-primary illness was defined as enteritis beginning in a contact of the index on the index date. Illness which began in a contact "before" was defined as enteritis beginning on any day prior to the index date which continued into the week before the index date. A contact was defined as developing enteritis after the index date if his/her symptoms began at least one day "after" the index date until the day of interview (case contacts) or during days 8-21 prior to the index date (control).

Table 46. The Relative Risk Associated with Contact with a Household Member Ill with Enteritis.

Timing of illness in household member	Enteritis in Household Contact: Yes Case	Yes Ctrl	No Case	No Ctrl	RR(95%CI)	P
7 days before	36	49	180	471	1.9(1.2-3.0)	0.005
On index date	9	1	206	521	22.8(5.4-95.9)	0.00002
After index date	70	63	144	456	3.5(2.4-5.1)	0.00000

Information was unknown for 9-11 cases and 4-7 controls.

The probability value from the chi-square statistic with 1 degree of freedom.

While cases were more likely than controls to report illness in their household contacts at any time before, during, or after the index date, note that the evidence for common source household outbreaks involving more than one member was stronger than that for person-to-person spread. A substantially greater propor-tion of cases than controls reported enteric illness developing in their household contacts on the index date (RR=22.8, 95%CI=5.4-95.9) whereas only 10% more cases than controls recognized illness which began in their household contacts in the week before the index date (RR=7.9, 95%CI=1.2-3.0). All ages of household members including parents, spouses, and siblings (except those 10-19 years) were reported to share in these outbreaks.

The laboratory provided supporting evidence for both person-to-person transmission among household members and common-source outbreaks. Culture positive contacts included: two siblings, a child, and the mother of several cases who had illnesses which preceeded the index date by at least one day. Eight family members became ill at least two days following the index date and were infected with C. jejuni at the time of culture.

Four household contacts, 3 children, and 1 spouse gave no history of symptoms but were infected with C. jejuni.

Age or relationship to the index subject of the household contact appeared to have little influence on the likelihood of a co-primary illness in a household contact. Nor did the contact's age affect the risk of transmission of C. jejuni infection to the index.

Persons unsure of any one, but not all, individual household contact's age or illness status were included in the following 9 tables as not having contact with an ill household member.

Table 47. Relative Risk Associated with Contact with Household Member Ill with Enteritis in the 7 Days Before the Index Date (Stratified by Contact's Age).

	Enteritis in Household Contact: Yes		No		
Contact's Age	Case	Ctrl	Case	Ctrl	RR(95%CI)
Infant	3	0	213	520	Inf(≥28.0)
1-4 year old	5	8	211	512	1.5(0.5-4.7)
5-9 year old	6	5	210	515	2.9(0.9-9.3)
10-19 year old	4	7	212	513	1.4(---)
20-39 year old	16	27	200	493	1.5(0.8-2.8)
≥40 year old	7	9	209	511	1.9(0.7-5.1)

1)Information was unknown for 9 cases and 6 controls.
2)Chi-square statistic for heterogeneity of relative risk across tables with 5 degrees of freedom=6.4, P=0.27.

Furthermore, when the analysis was stratified by the relationship of the contact to the index subject, prior illness in the offspring or housemate of the index was associated with 200% and 400% increase respectively, of the risk in the exposed when compared to the risk in those without such contact (child, RR=3.1, 95%CI=1.3-7.6; housemate, RR=5.0, 95%CI=1.7-14.9).

Table 48. Relative Risk Associated with Contact with a Household Member Ill with Enteritis in the 7 Days before the Index Date (Stratified by the Contact's Relation to the Index Subject).

Contact's Relationship to the Index	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)
Spouse/partner	6	8	210	512	1.8(0.6-5.3)
Parent	8	21	208	499	0.9(0.4-2.1)
Child	10	8	206	512	3.1(1.3-7.6)
Sibling	5	11	211	509	1.1(0.4-3.2)
Other relatives	1	3	215	517	0.8(0.1-7.7)
Housemate	8	4	208	516	5.0(1.7-14.9)

1)Information was unknown for 9 cases and 6 controls.
2)Chi-square statistic for heterogeneity with 5 degrees of freedom=9.6, P=0.09.

With respect to the occurrence of enteric illness in the household contacts after the index date, all age groups were recognized to receive the infection with the exception of children ages 5-9 years of age. Spouses/partners (RR=9.3, 95% CI=4.3-20.2), and housemates (RR=3.8, 95% CI=1.4-10.0) appeared to be the most commonly reported to be ill after the index date. Illness in siblings, and parents after the index date was reported more than twice as often by cases as by controls.

Table 49. Relative Risk Associated with Contact with a Household Member Who Became Ill after the Index Date (Stratified by the Contact's Age).

Contact's Age	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)
Infant	8	6	206	513	3.3(1.2-9.1)
1-4 year old	8	14	206	505	1.4(0.6-3.4)
5-9 year old	5	15	209	504	0.8(0.3-2.2)
10-19 year old	9	2	205	517	11.3(3.3-38.9)
20-39 year old	35	31	179	488	3.1(1.9-5.0)
≥40 year old	15	4	199	515	9.7(3.9-24.4)

1)Information was unknown for 11 cases and 7 controls.
2)Chi-square statistic for heterogeneity of relative risk across tables with 5 degrees of freedom=21.7, P=0.001.

Table 50. Relative Risk Associated with Contact with a Household Member Who Became Ill with Enteritis after the Index Date (Stratified by the Contact's Relationship to the Index).

Relationship	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)
Spouse/partner	21	6	193	513	9.3(4.3-20.2)
Parent	20	21	194	498	2.5(1.3-4.5)
Child	11	18	203	501	1.5(0.7-3.2)
Sibling	15	13	199	506	2.9(1.4-6.1)
Relative	2	4	212	515	1.2(0.2-6.7)
Housemate	9	6	205	513	3.8(1.4-10.0)

1)Information was unknown for 11 cases and 7 controls.
2)Chi-square statistic for heterogeneity across tables with 5 degrees of freedom=13.4, P=0.02.

Non-household contacts

With respect to non-household contacts, a higher proportion of cases than controls reported contact with individuals outside of their own households who were ill with enteritis in the week before the index date (RR=2.5, 95% CI=1.6-4.0). Even though very few non-household contacts were cultured, one friend of a case who had had an onset several months prior to that in the case was successfully cultured for C. jejuni at the time of the study.

Cases were three times more likely than controls to report enteric illnesses in their non-household contacts beginning on the index date. This difference, however, was not statistically significant (RR=3.1, 95% CI-0.9-11.0). There was little difference in illness in non-household contacts after the index date observed by either group.

Table 51. Relative Risk Associated with Contact with Non-Household Individuals Ill with Enteritis.

Timing of the Contact's Illness	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
In the 7 before the index date	37	41	153	421	2.5(1.6-4.0)	.0002
On the index date	5	4	184	458	3.1(0.9-11.0)	.18
After the index date	17	54	122	339	0.9(0.5-1.6)	.65

1)Information was unknown for 35-36 cases and 64 controls for the first two exposures and was unknown for 86 cases and 133 controls for the last exposure. Information about illness in non-household contacts after the index date was not obtained during the first four months of interviewing.
2)The probability value from the chi-square statistic with 1 degree of freedom.

While contact with individuals outside of the index household appeared to account for some of the C. jejuni cases in the GHC population, the proportion was low.

Cases reported contact with school-age children and adults over 39 years of age who were ill with enteritis prior to the index date significantly more often than did controls. However, cases reported prior enteric illness in every age group of non-house contacts more often than did controls.

Persons unsure of any one, but not all, individual non-household contact's age or illness status were included in the results as not having contact with an ill household member.

Table 52. Relative Risk Associated with Contact with Non-household Individuals Who Became Ill with Enteritis in the 7 Days before the Index Date (Stratified by Contact's Age).

Contact's Age[1]	Exposed		Unexposed		RR(95%CI)	p[2]
	Case	Ctrl	Case	Ctrl		
Infant	2	3	188	459	1.6(0.3-9.7)	.90
1-4 year old	3	5	187	457	1.5(0.4-6.2)	.86
5-9 year old	5	2	185	460	6.3(1.5-26.6)	.04
10-19 year old	5	4	185	458	3.1(0.9-11.0)	.18
20-39 year old	14	19	176	443	1.9(0.9-3.8)	.18
≥40 year old	9	6	181	456	3.6(1.4-9.7)	.02

1)Information was unknown for 35-36 cases and 64 controls.
2)The probability value from the Fisher's Exact Test or the chi-square statistic with 1 degree of freedom.

Table 53. Relative Risk Associated with the Contact with Non-household Individuals Who Became Ill with Enteritis in the 7 Days before the Index Date (Stratified by the Contact's Relationship to the Index Subject).

Relationship	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Relative	10	8	180	454	3.2(1.3-7.8)	.02
Friend	16	15	174	447	2.8(1.4-5.6)	.01
Co-worker	6	13	184	449	1.1(0.4-3.0)	1.00
Teacher/caretaker	1	1	189	461	2.5(0.2-36.1)	1.00
Boy/girl friend	2	0	188	462	Inf(≥3.9)	.16
Child cared for	2	2	188	460	2.5(0.4-16.5)	.33
Adult cared for	2	2	188	460	2.5(0.4-16.5)	.33
Other	4	0	186	462	Inf(≥110)	.25

1)Information was unknown for 35 cases and 64 controls.
2)The probability value from Fisher's Exact Test or the chi-square statistic for heterogeneity with 7 degrees of freedom=10.6, P=0.16.

Controls were more inclined to report having contact with individuals outside of their residence who became ill with enteritis after the index date than were cases. The only exception was contact with 20-39 year old co-workers who became ill with enteritis. Such contact was reported roughly twice as often by cases as by controls, but this difference could have been due to chance. (Co-workers, RR=2.3, 95%CI=0.9-5.9).

Table 54. Relative Risk Associated with Contact with Non-household Individuals Who Became Ill with Enteritis Beginning <u>after</u> the Index Date (Stratified by Contact's Age).

Contact's Age	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P[2]
Infant	0	7	139	386	0.0(---)	.24
1-4 year old	1	6	138	387	0.5(0.1-3.7)	.83
5-9 year old	1	4	138	389	0.7(0.1-6.3)	1.00
10-19 year old	1	8	138	385	0.3(0.0-2.6)	.54
20-39 year old	11	16	128	377	2.0(0.9-4.4)	.08
≥40 year old	8	16	131	377	1.4(0.6-3.4)	.41

1)Information was unknown for 86 cases and 133 controls.
2)The probability value from Fisher's Exact Test or trhe chi-square statistic with 1 degree of freedom.

Table 55. Relative Risk Associated with Contact with Non-household Individuals Who Became Ill with Enteritis Beginning after the Index Date (Stratified by the Relationship of the Contact to the Index).

Relationship	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR[1](95%CI)	p[2]
Relative	5	16	134	377	0.9(0.3-2.4)	.81.
Friend	6	21	133	372	0.8(0.3-2.0)	.64
Co-worker	8	10	131	383	2.3(0.9-5.9)	.07
Teacher/caretaker	0	1	139	392	0.0(---)	1.00
Boy/girl friend	1	0	138	393	Inf(≥0.2)	.52
Child cared for	1	2	138	391	1.4(0.1-15.6)	.59
Adult cared for	0	4	139	389	0.0(---)	.59
Other	0	4	139	389	0.0(---)	

1)Information was unknown for 86 cases and 133 controls.
2)The probability value from Fisher's Exact Test or the chi-square statistic with 16 degrees of freedom.

In general, contact with a child under 5 years who attended a day-care center was not associated with an increase in the risk of C. jejuni infection (RR=0.7, 95%CI=0.5-1.0). An attempt was made to determine if any individual day-cares may have been involved in outbreaks. Unfortunately, subjects who reported contact with children in day-cares were not always able to recall any more than the general location of the center. For that reason, the locations of the day-cares, using the division of the county as established in the King County Atlas were utilized in order to detect any potential day-care-associated outbreaks.

The day-care locations screened as potential outbreaks sources were those in which at least four contacts of cases or the cases themselves attended. The first was located in the Kirkland area (King County location 10, RR=7.7, 95% CI=1.1-52.8) and the second in W. Seattle (King County location 33 RR=10.4, 95% CI=1.8-61.2). In both locations, two index subjects subsequently infected with C. jejuni were in contact with children who either attended the same day-care or were cared for within 2 blocks of one another. The remaining index subjects who were in contact with children in day-cares in those locations could not recall the names of the day-cares. Only persons under 10 years of age reported contacts who attended day-care in Kirkland.

Table 56. Locations of day-care attended.

County Location	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Lake Forest Park	4	9	187	476	1.1(0.3-3.7)	.84
Northgate	8	16	184	470	1.3(0.5-3.0)	.58
Kirkland	3	1	189	484	7.7(1.1-52.8)	.14
University Area	5	13	186	472	1.0(0.3-2.8)	.96
Downtown Seattle	6	11	186	475	1.4(0.5-3.8)	.52
Mercer Island	4	6	187	479	1.7(0.5-6.0)	.41
W. Seattle	4	1	187	484	10.4(1.8-61.2)	.04
Snohomish, Location 78--inside study area	4	13	187	472	0.8(0.3-2.4)	.66

1)Information about day-care contacts was unknown for 25 cases and 18 controls. Locations of some of the day-cares attended by contacts were unknown for an additional 8-9 cases and 22-23 controls.
2)The probability value from Fisher's Exact Test or the chi-square statistic with 1 degree of freedom.

g. Animal exposures.

Contact with seven general types of animal was examined for its potential role in the transmission to humans of Campylobacter jejuni. The types of animals were: lab, pet, farm, feral, domestic, zoo, and exotic. Among these, only direct or indirect contact with zoo animals was more common among cases than controls (RR=3.0, 95% CI=1.0-8.5).

Table 57. Relative Risk Associated with Contact with General Types of Animal.

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Direct or indirect (shared premises, or cleaned the animal's quarters) contact with:						
Any animal	172	464	40	61	0.6(0.4-0.9)	0.01
Pets	166	458	46	67	0.5(0.4-0.8)	0.002
Zoo animals	7	6	205	519	3.0(1.0-8.5)	0.04
Unknown						

1)Information was unknown for 13 cases and 1 control.
2)The probability value from the chi-square with 1 degree of freedom.

As can be seen on the following two tables, no contact, either direct or indirect, with any given animal species resulted in an increase in the risk of C. jejuni infection unless the animal was ill with diarrhea within the 7 days prior to the index date (RR=4.3, 95% CI=1.9-9.7). Cases were more likely than controls to have reported contact with a diarrheic dog (RR=11.5, 95% CI=2.0-65.9) or puppy (RR=8.6, 95% CI=1.3-57.0). Cases were at least more likely than controls to report contact with a diarrheic pet bird or kitten although there were only 4 cases who reported such exposures. Subject's whose contact with a particular species did not involve touch were excluded from the following table.

Table 58. Relative Risk Associated with Direct Animal Contacts as Contrasted with No Direct Contact with That Particular Species.

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Dog	117	327	90	194	0.8(068-1.1)	.12
Cat	96	287	113	235	0.7(0.5-1.0)	.03
Bird	22	58	187	462	0.9(0.6-1.6)	.81
Reptile	1	8	206	518	0.3(0.0-2.3)	.45
Cattle	3	9	205	514	0.8(0.2-3.1)	.79
Sheep	2	5	206	519	1.0(0.2-5.2)	1.00
Pig	2	4	205	518	1.3(0.2-6.9)	1.00
Goat	1	11	206	512	0.2(0.0-1.5)	.12
Fish	7	18	200	504	1.0(0.4-2.4)	.96
Rodent	9	30	198	491	0.7(0.3-1.6)	.45
Other animals	18	54	189	469	0.8(0.5-1.4)	.51

1)Information was unknown for 6-8 cases and 0-6 controls.
2)The probability value from Fisher's Exact Test or the chi-square statistic with 1 degree of freedom.

While several animal contacts were successfully cultured for C. jejuni including four cats, five dogs, two calves, several goats, chickens, and one duck, only one puppy from whom C. jejuni was isolated by us was known to be ill prior to the index date. Several days prior to her onset, one adult case visited a friend's home, petted the cat who was home alone, and left. The cat was subsequently found by us to be carrying C. jejuni in it's stools. It's owner had been ill with an undiagnosed enteric illness.

Finally, as limited support of human to animal trasmission, one dog developed diarrhea after the index date and was successfully cultured for C. jejuni.

Persons unsure of any one, but not all, individual animal contacts' ages or illness status were included in the unexposed category in the following 3 tables.

Table 59. Relative Risk Associated with Contact with Animals Who Were Ill with Enteritis in the 7 Days before the Index Date.

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Any animal	13	9	145	434	4.3 (1.9-9.7)	.0009
Any age dogs	7	2	151	441	10.2(2.8-37.1)	.004
Adult dogs	4	1	154	442	11.5(2.0-65.9)	.02
Puppies	3	1	155	442	8.6(1.3-57.0)	.12
Any age cats	3	7	155	436	1.2(0.3-4.7)	1.00
Adult cats	1	7	157	436	0.4(0.1-3.0)	.66
Kittens	2	0	156	443	Inf(≥7.8)	.14
Pet birds	2	0	156	443	Inf(≥7.8)	.14

1)Information was unknown for 67 cases and 83 controls.
2)The probability value from the chi-square statistic with 1 degree of freedom.

While the numbers were small, 42.9% of the case infants as compared to 1.7% of the control infants were reported to have contact with an animal ill with enteritis in the week prior to the index date. For the remaining age groups, with the exception of the 10-19 year olds, roughly 4 times as many cases as controls reported contact with diarrheic animals in the week prior to onset/interview.

Table 60. Relative Risk Associated with Contact with Animals who were Ill with Enteritis in the 7 Days Before the Index Date (Stratified by Age of Index)

Index Subject Age	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Infant	3	1	4	59	44.3(8.0-243.8)	.00001
1-19	1	3	36	125	1.2(0.1-11.5)	1.00
≥20	9	5	105	250	4.3(1.5-12.1)	.01

1)Information was unknown for 67 exposed cases and 83 exposed controls.
2)The probability value from Fisher's Exact Test or the chi-square statistic with 1 degree of freedom.

Neither cases or controls recognized any illness in animal contacts beginning on the index date. Human-to-animal transmission was also not recognized to have occurred in any significant proportions.

Table 61. Relative Risk Associated with Contact with Animals Who Became Ill with Enteritis after the Index Date.

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Any age dogs	2	3	153	444	1.9(0.3-11.3)	.76
Adult dogs	2	3	153	444	1.9(0.3-11.0)	.76
Any age cats	2	5	153	442	1.2(0.2-6.0)	1.00
Adult cats	1	3	154	444	1.0(0.1-9.3)	1.00
Kittens	1	2	154	445	1.4(0.1-15.9)	1.00

1)Information was unknown for 70 cases and 79 controls.
2)The probability value from Fisher's Exact Test.

h. Miscellaneous exposures.

A greater proportion of controls than cases had non-municipal as opposed to other types of sewage treatment (RR=0.6, 95% I=0.4-0.9). This was partially, if not wholly, explained by the greater representation in the control group of rural GHC Enrollees.

Travelers who experienced plumbing problems while on their trips were at greater risk of C. jejuni infection than the non-travelers or the travelers who did experience such problems (RR=13.1, 95% CI=1.3-65.2). This effect occurred primarily in U.S. travelers. Two of the eight cases who traveled to an undeveloped foreign nation also reported such problems.

Plumbing problems at home were reported almost twice as often by cases as by controls although this difference could be due to sampling variability (RR=2.0, 95% CI=0.9-4.0).

Table 62. Relative Risk Associated with Specific Types of Sewage Treatment or Problems in the 7 Days Before the Index Date.

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Non-municipal (i.e., septic, cesspool, chemical or other)	28	109	181	405	0.6(0.4-0.9)	.02
Plumbing or sewage backed up	13	17	199	507	2.0(0.9-4.0)	.07
Plumbing or sewage backed up while on a trip of $\geq$ 30 miles[1]	5	1	164	422	13.1(1.3-65.2)	.02

1) Adjusted for travel to undeveloped foreign nation+.
2)The probability value from Fisher's Exact Test or the chi-square statistic with 1 degree of freedom.

The handling of fecal matter, or toilet water contact (as with infants) was reported equally by cases and controls. The exposures, however, were only ascertained for roughly the last eight months of the interviewing.

Table 63. The Relative Risk Associated with Contact with Sewage in the 7 Days before the Index Date.

Exposure	Case	Ctrl	RR(95%CI)
Any sewage contact	14	34	1.1(0.5-2.1)
No toilet water or sewage contact/ingestion	85	218	1.0
Unknown	126	274	
Total	225	526	

1)Overall Chi-square statistic with 1 degree of freedom=0.0.3, P=0.87.

Among other miscellaneous exposures, antibiotic use prior to onset/interview, smoking marijuana or cigarettes, use of a vegetable garden, use of manure for gardening, and animals defecating in the garden were reported equally by cases and controls.

Table 64. The Relative Risk Associated with Miscellaneous Exposures.

Exposure	Exposed Case	Exposed Ctrl	Unexposed Case	Unexposed Ctrl	RR(95%CI)	P
Antibiotic used	12	26	204	498	1.1(0.6-2.3)	0.74
Smoked cigarettes	34	76	136	263	0.9(0.5-1.4)	0.53
Smoked marijuana	15	25	154	313	1.2(0.6-2.4)	0.56
Information was unknown for 7-56 cases and 2-188 controls.						
The following exposures apply if food eaten in the 7 days before the index date was from the index's garden.						
Ate food from own garden	40	108	172	415	0.9(0.6-1.3)	0.59
Used or handled manure in prior season	21	49	188	454	1.0(0.6-1.8)	0.89
Used commercial fertilizer	16	64	190	445	0.6(0.3-1.0)	0.06
Animals defecated in garden	18	52	188	455	0.8(0.5-1.5)	0.54

1)Information was unknown for 13-19 cases and 2-23 controls.
2)The probability value from the chi-square statistic with 1 degree of freedom.

8. Etiologic Fraction--Proportion of GHC C. jejuni Incidence Attributable to Each of the "Causal Exposures"

For exposures which had been previously implicated as causal by other investigators or for which there was supporting laboratory evidence and which were associated with at least an 80 percent increase in the risk of C. jejuni infection to the exposed (based on a relative risk of $\geq$1.8) were defined as causal exposures. We sought to estimate the magnitude of the incidence within the GHC membership etiologic fraction for which each one was responsible.

Table 65. Etiologic Fraction (lambda) and Relative Risk Associated with the Suspected Causal Exposure Variables for *C. jejuni* Infection.

Exposure in 7 Before Index Date	RR(95% CI)	Lambda
Travel to undeveloped nations	36.9(10.2-133.6)	9.0%
Travel to Mexico*	Inf(---)	4.7%
Raw milk	4.6(2.1-10.4)	5.2%
Unprocessed chicken	2.4(1.6-3.6)	48.2%
Non-home surface or well water	1.8(1.1-2.9)	7.6%
Household member ill with enteritis	1.9(1.2-3.0)	8.0%
Non-household member ill with enteritis	2.5(1.6-4.0)	11.7%
Any animal ill with enteritis	4.3(1.9-9.7)	6.3%
Canine ill with enteritis	12.0(2.1-67.9)	4.2%

*Test-based confidence limits could not be determined, probability value from chi-square statistic with 1 degree of freedom=0.0000.

a. Foods

The exposure to which the greatest proportion of the C. jejuni cases could be attributed was chicken consumption (lambda=48.2%). 5.2 percent of the GHC C. jejuni incidence was attributable to raw milk consumption.

b. Person-to-Person Transmission

Person-to-person transmission via contact with household and non-household members who were ill with enteritis could be responsible for 8.0 and 11.7 percent of the C. jejuni cases. Contact with humans or animals ill with enteritis during the week prior to, but not beginning on, the index date was assumed by us to be a potential source of C. jejuni infection for the cases. This assumption was based on the incubation period for C. jejuni. Illnesses beginning in contacts on the index date were defined as co-primary illnesses.

c. Animal-to-Human Transmission

Direct contact with diarrheic animals appeared to play a role in 6.3 percent of the GHC C. jejuni incidence. Diarrheic dogs were implicated in more cases than any other species although birds and kittens may play a slight role as well.

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d. Travel and Water

4.7 percent of the C. jejuni cases were acquired while traveling in Mexico and 9.0 percent while traveling in any undeveloped nation, including Mexico, India, and China.

Whereas water consumed while away from home and work in some of the more rural counties of Washington State, such as Island, San Juan, Okanogan, and Whatcom counties, was consumed significantly more often by cases than by controls overall, the increased risks associated with the drinking of surface, well, and bottled waters did not differ significantly from unity at $P \leq .05$.

As water has been implicated as a potential source of contamination in several outbreaks (45) and C. jejuni has been isolated from many enviornmental waters (10, 45), we chose to estimate the proportion of the incidence attributable to drinking water. In order to do so, whether or not well or surface, water was consumed while at least 30 miles away from home was determined. Water consumed at work or in the course of communting regularly was not counted as an exposure. 7.6% of the GHC C. jejuni incidence was attributable to drinking such waters.

9. Strain-specific Risk Factor Analysis.

The risk factors for tetracycline sensitive and resistant C. jejuni infections did not differ
with one possible exception.
A greater proportion of tetracycline resistant as opposed to sensitive infections were attributable to drinking raw milk (RR=8.5, Lambda=39.5% vs. RR=2.5, Lambda=21.2%).

Table 66. Relative Risks Associated with Causal Exposures for Tetracycline Sensitive and Resistant Strains.

Exposure	Tetracycline Sensitive			Tetracycline Resistant			
	Exp.	Unexp.	RR(95%CI)	Exp.	Unexp.	RR(95%CI)	P
Travel to undeveloped nations	9	132	35.7(9.7-132.0)	4	56	37.4(9.4-148.3)	0.94
Chicken	111	24	2.1(1.3-3.5)	50	8	2.9(1.4-6.1)	0.50
Raw Milk	5	130	2.5(0.8-7.4)	7	53	8.5(3.5-20.8)	0.03
Domestic Fowl	5	133	3.6(1.1-11.6)	2	58	3.3(0.7-15.7)	1.00
Well or Surface Water	20	105	1.7(1.0-3.0)	10	44	2.1(1.0-4.3)	0.68
Contact with Ill Household Members	25	116	2.1(1.2-3.5)	8	53	1.5(0.7-3.2)	0.42
Contact with Ill Animals	7	94	3.6(1.4-9.3)	3	43	3.4(0.9-12.0)	0.93

1)The probability values based on the chi-square statistic with 1 degree of freedom derived from the comparison of exposed and unexposed cases in both groups.
2)Cases who reported some of the above exposures but whose isolates were not tested for tetracycline response were excluded from the above analysis.

Interest in whether or not C. jejuni and C. coli represent differeing epidemiologic pathways led us to analyze the risk factors for each separately. Unfortunately, only 11 cases were infected with hippurate negative strains which limited any inferences which could be gleaned from such a contrast.

Table 67. Relative Risks Associated with Causal Exposures for Hippurate Positive and Negative Strains.

Exposure	Hippurate Negative (*C. coli*)			Hipputate Positive (*C. jejuni*)			
	Exp.	Unexp.	RR(95%CI)	Exp.	Unexp.	RR(95%CI)	P
Travel to Undeveloped Nations	3	8	196.5(72.1-535.7)	10	180	29.1(7.5-113.2)	.004
Chicken	10	0	0.0(≥2.9)	151	32	2.2(1.4-3.3)	.18
Raw Milk	0	10	0.0(---)	12	173	4.5(1.9-10.3)	.41
Domestic Fowl	1	10	9.5(1.5-59-6)	6	181	3.1(1.0-9.8)	.66
Well or Surface Water	2	8	2.3(0.5-10-6)	28	141	1.8(1.1-3.0)	.78
Contact with Ill Household Members	4	8	4.8(1.6-14.8)	29	161	1.7(1.1-2.8)	.10
Contact with Ill Animals	0	9	0.0(---)	10	128	3.8(1.6-8.9)	.40

1)Probability values based on the chi-square statistic with 1 degree of freedom derived from the comparison of exposed and unexposed cases in both groups.
2)Cases who reported some of the above exposures but whose isolates were not tested for hippurate hydolysis are excluded from the above analysis.

10. Comments on Case/control Study

a. Comparability of Cases and Controls.

A common concern in case-control studies of this nature is that the cases and controls may lack comparability in ways which could potentially bias the analysis. Thus, the differences measured between case and control subjects, although real, could be entirely unrelated to the etiology of the disease under investigation.

As both cases and controls were selected from the GHC population, the potential for such bias was reduced. However, a remaining concern regarding comparability was that either cases or controls might participate more fully due to differential access to medical care. For example, well individuals who visit GHC regularly, who have a strong interest in health-related issues and who have a different underlying lifestyle or health status than the GHC population-at-large might be more inclined to participate. All C. jejuni patients, however, as they were quite ill and were identified universally regardless of their historic use of GHC, could have more accurately represented all C. jejuni cases occurring among GHC enrollees during the period of interest. The potential for differential access to medical care was somewhat reduced in this study due to the relatively homogeneous access available to the enrollee's of GHC.

Furthermore, all subjects were queried as to the number of well care visits they had had in the year prior to their onset or interview and no differences between cases and controls were observed.

b. Limitations

Some of the limitations of this study include:

1. The sensitivity of stool sampling of both animal and human contacts may have been somewhat reduced due to an average two week time delay after the onset of symptoms in the index cases.

2. The likelihood that C. jejuni infections in human beings arise from multiple pathways suggests that the risk of infection resulting from any one exposure may be only slightly elevated and not detectable in a study of this size.

3. The examination of the risks associated with multiple exposures increased the likelihood of statistically significant association in the absence of a real association. However, scientific signficance and support for a cause and effect relationship do not depend solely on statistical significance but also require careful examination of the magnitude of an effect, a temporal relationship between the exposure and outcome, biologic plausibility and consistency of evidence within and across studies.

4. The broad ranging incubation period of C. jejuni infection increases the opportunity for misclassification of exposures and dilution of differences between cases and controls and a conservative estimate of the risks associated with the various exposures. For example, some of the animal and human contacts may have been labelled as having an illness which preceeded that occuring in the index subject but which was in fact a co-primary illness or vice versa.

5. The controls participated less fully than did the cases, and concerrn arises that they may not accurately reflect the under-

lying GHC population. Unequal response rates between cases and controls does not of itself result in a bias any more than equivalent response rates ensure representativeness or comparability. If the exposure rates in the non-respondents do not differ from those in the controls no bias would occur. We have carefully determined in what ways our controls may differ from the GHC population by interviewing a significant proportion of the non-respondents. Had all eligible GHC enrollees selected for interview agreed to participate, our results may have differed in the following ways:

i. Relative risk associated with rural water supplies and sewage systems as compared to municipal systems would have been closer to unity as the participating controls better represented the more rural areas.

ii. The increase in risk associated with travel to undeveloped nations, and Island and Okanogan County would have been even greater as none of the non-respondents visited these areas.

iii. Four non-respondents visited Canada (5.2%) as compared to 6 controls (12.1%). Thus, the protective effect of travel to developed nations would have been slightly greater.

iv. The risk estimate associated with outdoor activity in remote areas would have been closer to unity.

v. The increase in risk associated with raw milk consumption could have been slightly reduced as 3 non-respondents reported consuming raw milk. Assuming the remaining GHC enrollees who originally declined to be interviewed would have responded similarly, the risk in the exposed would have been

closer to 3.4 (95% CI = 1.7-7.0) and the etiologic fraction 4.7%.

vi. The risk of C. jejuni infection associated with chicken eating would have been even greater (RR=4.0, 95%CI≥64.1) as non-respondents reported chicken consumption less often than did controls. None of the other factors would have been impacted in any way.

vii. Greater recognition of illness in contacts similar to that in themselves may explain some of the differences between cases and controls with regard to reporting of ill animal and human contacts, especially that of non-household contacts where knowledge of a contact's health status may be less precise.

6. Cases frequently are better able to recall exposures which may artificially inflate measured risks and diminish protective effects (Sackett DL, Bias in analytic research. J Chronic Diseases 1979. 32:51-68.) In this study, however, cases had to recall exposures ocurring an average of 2 - 3 week prior to the interview as compaed to only 1 week recall required of control subjects. This hopefully helped to reduce the differential recall between cases and controls.

7. Occupational differences between the heads of case and control households may reflect between access or concern for medical care rather than true occupational risk of acquiring C. jejuni infection. For example, while it is reasomable that teachers and physicians might have greater risk of person-to-person spread, they also may be more likely to pursue to diagnosis enteric infections occuring within their households thus recognizing them when others may not. Additionally,

engineers, teachers, and physicians may be less motivated to participate as controls than perhaps some of the other professionals resulting in an inflated risk estimate.

VI. DISCUSSION

Details of the total scope of work performed under Contract #223-81-7041 can appropriately be discussed in relation to the four stipulated objectives of the contract. One objective was to determine the magnitude and the character of the problem of human illness caused by Salmonella and C. jejuni in a defined population. The present study was well designed to accomplish that objective, because its case-surveillance system was established at Group Health Cooperative of Puget Sound (GHC), a 320,000 member health maintenance organization serving residents of western Washington. Surveillance of the two diseases of interest at GHC permitted the derivation of incidence rates because of the availability of patient enrollment statistics to serve as denominators to match case information or numerator data.

The overall incidence of C. jejuni infection at GHC was 71.5 cases diagnosed per 100,000 population per year, some two and one-half times the incidence of Salmonella infection (27.7/100,000/year). Other investigators have reported C. jejuni infections to be more frequent than salmonellosis (11, 46), and this newly recognized infection may in fact, be more common than the two traditionally predominant bacterial infections, salmonellosis and shigellosis combined (46).

Only two reportable diseases, gonorrhea, with an incidence of 415 per 100,000 and chicken pox, with a rate of 72.2 per 100,000, were reported in the U.S. in 1982 at an incidence greater than that of C. jejuni (47). To provide further com-

parison, in 1982 the incidence of tuberculosis in the U.S. was 11.0 per 100,000, that of syphilis, 32.7 per 100,000 (47).

A difference was also noted in the age-specific incidence of C. jejuni infection as compared to that for salmonellosis. Along with a peak in incidence in infants, very similar to that of Salmonella infection, there was with C. jejuni a second distinct peak in the young adult years, ages 20-39, which was entirely absent in salmonellosis.

This distinctive diphasic curve that comprises the age-specific incidence for C. jejuni infections has also been noted in Great Britain (48). The absence of a male preponderence of cases within the peak in the young adult years suggests that male homosexuals, known to acquire C. jejuni anorectal infections (49), do not account for a large proportion of cases in the GHC population. Nevertheless, this observed difference between C. jejuni and Salmonella age-specific rates suggests fundamental differences in the epidemiology of the two infections, which are currently viewed by many to have common pathways of transmission to and among humans.

Clinically, C. jejuni and Salmonella enteritis produced illnesses that were virtually indistinguishable. Nearly all patients with both infections had diarrhea and cramps, with a substantial minority suffering from bloody diarrhea. Fortunately, it was necessary to hospitalize only a small fraction of patients with both infections, and none died.

In comparing the morbidity of C. jejuni and Salmonella enteritis two facts suggested that the former was more severe.

First, a significantly larger proportion of patients with C. jejuni infection experienced weight loss with their illness, and secondly, the mean duration of symptoms was significantly longer.

One estimate of the magnitude of the problem caused by C. jejuni is a derivation of days lost to normal activities due to the infection. The mean duration of C. jejuni illness was 13.52 days in the present study. If it is assumed that approximately half of that time, or 7 days, was lost to normal activity such as employment, then one can calculate that 40 person-weeks of normal activity would be lost per 100,000 population per year due to C. jejuni infection. In a city of one million population, therefore, 400 person-weeks or 7.69 person-years of normal activity such as employment, would be lost due to this infection.

Furthermore, if it is true that C. jejuni infection is more prevalent than salmonellosis and produces as great or greater morbidity, then it is possible to make crude estimates on the importance of C. jejuni infection based upon statistics derived for salmonellosis. For example, it has been estimated by the Centers of Disease Control that as many as two million cases of salmonellosis occur annually in the U.S., at a cost of more than a billion dollars to the U.S. economy (1). An infection such as C. jejuni enteritis, which occurs twice as frequently as salmonellosis and is at least as severe, might be expected to produce an economic impact twice that of salmonellosis, or two billion dollars a year upon the U.S. As crude as these estimates are, it can be appreciated that the potential quantitative impact of C. jejuni upon a population similar to that where the current case sur- veillance system was conducted is considerable whether

viewed in terms of disease morbidity or economic burden.

It should be kept in mind that all the foregoing estimates were made without consideration of related C. jejuni infections within a family. Our culture surveillance in family contacts of cases and our case/control study documented that the organism is prevalent in the environment of cases, and that contacts of cases are at increased risk for the illness, but the morbidity associated with these findings is yet to be determined.

Two of the three remaining objectives of Contract #223-81-7041 may be considered together as a basis for further discussion of the present study because the two objectives are closely related. The first was to define the character of the movement of bacteria from animals to man, using as markers Salmonella and C. jejuni in foods from animals; the second, to utilize specific microbiological markers to link human illness caused by Salmonella and C. jejuni to specific animal sources. With respect to the use of C. jejuni and Salmonella as "markers" for bacterial contamination of animal-derived food, the present study is the first, to our knowledge, to report comparative contamination rates for these two pathogens in the same pool of food products. C. jejuni was isolated over four times more frequently than Salmonella but was found almost exclusively in poultry products. Thus, in retail poultry at least, C. jejuni appears to provide a better marker for bacterial contamination than does Salmonella.

Because C. jejuni contamination of poultry products was the only significant positive finding in the food surveillance compo-

nent of this study, further discussion of possible linkages between food contamination and human illness will be restricted to considerations relating to that phenomenon.

Considerable effort was extended in the present project to characterize all C. jejuni isolates from food and human cases with respect to three specific microbiological markers which might, to paraphrase the contract objective under question, link a human illness, C. jejuni enteritis, to a specific animal source, poultry. The three markers were antibiotic susceptibility testing, plasmid analysis, and serotyping (as noted in Results Section H, serotyping of C. jejuni isolates was performed by the Centers for Disease Control, Atlanta, GA).

The most interesting observations to emerge from the study of these phenotypic markers of C. jejuni was a relationship between tetracycline resistance and plasmid carriage. First, a surprisingly high rate of tetracycline resistance was noted in poultry products (32.8%) and in human cases (29.7%). Secondly, there was a strong correlation between tetracycline resistance and plasmid carriage; 93% of tetracycline resistant strains harbored plasmids. Thirdly, 30 of 31 plasmid-containing isolates were able to transfer the tetracycline resistance phenotype, confirming the fact that the resistance gene is located on extrachromosomal elements. Finally, there were no differences in the MIC's of tetracycline for the isolates tested with and without pre-exposure to the antibiotic, which suggests that tetracycline resistance is not inducible in Campylobacter species, and therefore not located on the bacterial chromosome.

Previous work with R-factors obtained from cynomologous

monkeys (35) and Taylor and associates' early studies with human isolates (50) suggested that the R-factors mediating tetracycline resistance in C. jejuni would be of a single type and size, since both of the above reports describe a conjugal 57 kilobase plasmid. However, during the present study, it became apparent that C. jejuni plasmids both larger and smaller than 57 kilobase were capable of transferring resistance to tetracycline within Campylobacter species. Although the BglII and BclI endonuclease patterns of these plasmids were highly diverse, further analysis revealed that several fragments were highly conserved. These data confirm and extend the data recently published by Taylor and associates (50), who also noted a high degree of nucleotide homology among Campylobacter R-factors. Further studies are needed to explain the reasons for the diversity in size of these closely related C. jejuni plasmids.

Further work must also be done to determine the relationship between carriage of a tetracycline R-factor by C. jejuni and tetracycline supplementation of poultry feed; the present study did not address this issue directly. However, we did observe variation, unlikely to be due to chance, between tetracycline resistance of C. jejuni cultured from Washington-reared poultry and that of poultry originating in other states. It is tempting to speculate that geographic variability in plasmid mediated tetracycline resistance of C. jejuni could be related to regional differences in poultry feeding patterns. Further specific study should be undertaken to unravel any relationships that may exist between poultry feeding practices and C. jejuni plasmid profiles

and susceptibility patterns in a given region. It is noteworthy that the strain specific analysis preformed as a part of the case/control study showed that humans were no more likely to acquire tetracycline-resistant than tetracycline-susceptible C. jejuni infections from poultry. This finding suggests that poultry does not serve as the only reservoir of tetracycline-resistant C. jejuni infection.

Also yet to be determined is the clinical significance of tetracycline resistance in C. jejuni. Most patients with C. jejuni infection do not receive antibiotic therapy (51), and tetracycline is not the drug of choice should an antibiotic be needed (10). Furthermore, previous studies (50) and work done under the present contract all demonstrate that the C. jejuni R-factors could not be introduced into E. coli by conjugation or transformation. This suggests that these plasmids are incapable of replicating at least in E. coli and probably in the Enterobacteriaceae in general. Whether these plasmids could be transferred and maintained in other members of the bowel flora, such as in Bacteroides species, remains to be tested. It is possible, therefore, that there is little practical clinical significance to the finding of a related family of C. jejuni R-factors, even should they ultimately be traced to poultry feeding practices.

To conclude a review of microbiological markers identified in the present study, one other interesting phenomenon was noted: C. jejuni isolates from human cases and retail poultry possessed distributions of the six most frequent Lior serotypes that were virtually identical. This correlation has been noted previously with Salmonella serotypes isolated from human and non-

human sources (2), and has been used as evidence that human Salmonella infections arise from an animal reservoir, presumably through contamination of animal-derived food (3).

However, a word of caution must be raised against the casual use of microbiological markers to link bacteria from different sources, or more specifically, to prove that human C. jejuni infections arise from animal-derived food, as the two contract objectives under question stipulate.

The precedence for the use of phenotypic bacterial markers to identify sources of human disease originated with the study of foodborne outbreaks. In that setting, laborataory tests often show similarities between pathogenic bacteria isolated from food eaten by ill individuals and those isolated from the patients themselves. In fact, the investigation of the single C. jejuni foodborne outbreak in the present project (Appendix B) fit this pattern perfectly, with the outbreak-associated bacterial strains, isolated from all implicated patients and from several goats at the implicated dairy, showing virtual homology among the following tests: susceptibility to five antibiotics, plasmid pattern, and Lior serotype.

However informative bacterial phenotypic markers may be in the evaluation of foodborne outbreaks, it is quite a different matter to presume that they will be useful in identifying sporadic, isolated infections as being foodborne. Similar phenotypic markers in C. jejuni isolates from retail poultry and patients could, taken alone, as easily support a hypothesis that chickens were infected by humans, or perhaps more reasonably, that chick-

ens and humans derived their C. jejuni isolates from another large enviornmental reservoir.

For purposes of linking C. jejuni isolates from different groups, it would have been helpful had significant C. jejuni contamination of another type of meat been detected. In that case, isolates from humans could have been compared to those of the two meat species by analysis of the microbiological markers and perhaps subsequently labeled as more similar to isolates found in one meat species than to those of the other. This was not the case, although C. jejuni isolates from retail poultry did show closer marker similarities to human strains than did those from processor products.

This dilemma concerning appropriate interpretations of data on microbiological markers of C. jejuni was largely resolved by information gained from the case/control study of C. jejuni infections in humans. Case/control analysis is one of the tools routinely applied by epidemiologists to address questions of cause and effect in human disease. The dual approach employing microbiological and epidemiological (case/control) methodologies employed in this study has recently been proposed by the CDC to determine the cause(s) of sporadic cases of salmonellosis (correspondence from John C. Feeley, Acting Director, Division of Bacterial Diseases, CDC, to State and Territorial Epidemiologists dated June 6, 1984. Subject: Salmonella antimicrobial resistance patterns in the United States).

Because the epidemiology of human C. jejuni infection is so poorly understood, it was considered essential to explore numerous potential causal factors by means of an extensive inquiry

into the backgrounds of affected and unaffected persons. During this process, a wide variety of potential food exposures and habits were sought in order to maximize the likelihood of addressing a prime objective of Contract #223-81-7041, which was to link human illness caused by C. jejuni to specific animal sources through food derived from those animals.

There were a number of exposures that were more frequent among cases than among controls during the week prior to the onset of symptoms. Consequently those exposures were identified as potential causes of C. jejuni enteritis. It is noteworthy that many of the previously implicated types of transmission of C. jejuni infection to humans summarized from the literature in a recent epidemiological review (45) were also found to be risk factors for sporadic C. jejuni enteritis in the present study. Among those were travel to an undeveloped country, consumption of chicken, drinking raw milk, consumption of untreated surface water, contact with humans ill with enteritis, and contact with pets, particularly dogs, with diarrhea.

The most surprising food exposure found to have an elevated relative risk in the present study was mushroom consumption. Mushrooms have not previously been implicated as a vehicle for C. jejuni infection. However, that vegetable is grown commercially in high concentrations of animal manure, including that of chickens. Thus, C. jejuni proliferation is plausible in this setting. Furthermore, because mushroom eating is a common exposure, there is considerable potential profit for disease prevention in establishing a causal relationship. Further work should be done to

substantiate this finding.

Considering the objectives of Contract #223-81-7041, it is appropriate to focus critical attention upon chicken consumption, found in our study to have an elevated relative risk. Is this association, in fact, a causal one?

Several well-accepted observational criteria for causation of associations found in case/control studies (52) may be applied to that between eating chicken and C. jejuni enteritis. First, the temporal sequence must be consistent: a causal event precedes its effect. In the present study, the questions on food exposures applied specifically to the 7-day period prior to onset of illness. This time interval was chosen because existing information suggested that the incubation period for C. jejuni infection ranges between two and seven days. Assuming no recall bias was present, the temporal sequence criterion appears to have been satisfied for the association under question.

A second condition for causation is that the association under question should be consistently observed under different conditions. As previously noted, there is now an accumulating body of evidence that eating chicken is a risk factor for C. jejuni infection. Brouwer et al. (53) described an outbreak in a military academy which affected 89 of 123 first year cadets during a survival exercise. Each cadet had killed, skinned, and prepared his own chicken over a wood fire. In several recent case/control studies (24,25,54,55), the cases reported greater frequencies of chicken consumption (25,54,55), handling of chicken during meal preparation (24,55), and greater frequency of shorter cooking time (55), than did controls.

Thirdly, the strength of the association provides evidence for causation. In the present study, the relative risk for chicken consumption was not large, as cases were only two and one-half times as likely as controls to have named that exposure in the week prior to onset of illness. It is probable that the strength of the association would have been much greater had it been possible to ascertain the consumption of C. jejuni- contaminated chicken, found in our food surveillance study to represent approximately 22% of all retail specimens. According to this evidence, almost 80% of chicken eaters were not at risk for C. jejuni enteritis because the chicken that was eaten was not contaminated. This fact led to considerable dilution of the association between chicken consumption and C. jejuni enteritis, and produced the relatively modest relative risk.

A final important condition supporting causation of an observed association is consonance of the association with existing knowledge. It is in this context that the microbiological information acquired in our study assumes importance. The association of chicken eating with C. jejuni infection is strongly supported by the observation in this and previous studies (11-14) that retail poultry products are frequently contaminated with C. jejuni because this is a plausible mechanism by which eating chicken could "cause" C. jejuni infection.

Furthermore, the similarities in antibiograms, plasmid content, and serotypes of C. jejuni isolates from retail poultry and humans found in the present study would be expected should a substantial fraction of human C. jejuni infections derive from

the pool of organisms that are found in poultry. In addition, the similar seasonal patterns of C. jejuni contamination of retail poultry and human C. jejuni cases, with a summer-fall peak, is evidence for a causal association. It should also be noted that the absence of C. jejuni isolation from the other major meat species, beef and pork, supports the lack of association of those foods with C. jejuni illness in the case/control study.

The fourth and last objective of Contract #223-81-7041 was to determine the proportion of human salmonellosis and C. jejuni enterities which has its origin from animal foods obtained from poultry, swine, and beef. For C. jejuni this proportion was estimated, in the determination of the "etiologic fraction," to be 48.2% for poultry and none for either beef or swine.

The etiologic fraction of a disease is viewed as the expected reduction in the disease following removal of the exposure. Thus, we estimate that almost 50% of C. jejuni infections at Group Health Cooperative during the period of study would not have occurred had no poultry been consumed. We have no reason to believe that the same effect would not accrue to the general population if C. jejuni contamination of retail poultry were controlled.

Thus, work performed by Seattle-King County Health Department and its subcontractors under Contract #223-81-7041 provides an important insight into the epidemiology of infections due to Camplylobacter jejuni by showing that almost half of cases in a defined population over an 18-month period were attributable to eating poultry. This information, derived from the case/control

study, was supported by results of food surveillance showing that over 20 percent of poultry products sampled at King County retail outlets over the same period were contaminated with C. jejuni. Furthermore, C. jejuni isolates from those human cases and retail poultry were similar with respect to antibiotic susceptibilities, plasmid carriage, and serotype.

The food surveillance component of the present study suggested several possible strategies for at least reducing C. jejuni contamination of poultry. For example, isolation rates for C. jejuni in retail markets were lowest on Mondays, when display shelves were cleanest and products had been freshly received. On the other hand, handling of poultry at the retail level appeared to increase the likelihood of culturing C. jejuni. The most dramatic effect on C. jejuni contamination of poultry was movement of products from processor, where the isolation rates approached 60%, to retail sites, where it fell to just over 20%. Observations such as these provide hypotheses for studies aimed at reducing C. jejuni contamination in retail poultry.

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APPENDIX A

FORMS

PHONE CONTACT TO SOLICIT CASE INFORMATION (CAMPYLOBACTER)

Hello, my name is (insert name) from the Seattle-King County Health Department. I work as an epidemiologist/interviewer at Seattle-King County Department of Public Health. Group Health Cooperative of Puget Sound is participating in a project by reporting to us all the Campylobacter infections that occur in their patients. You may have received our letter about the study. Did you? Your practitioner, (insert name), agreed that I could talk to you about the recent illness for which he/she treated you. It is called a Campylobacter infection and it is spread in somewhat the same way as Salmonella, a more commonly known infection. It has only recently been learned that the Campylobacter bacterium is an important cause of diarrheal illness. This is why I am calling you. We are conducting an investigation of Campylobacteriosis. The purpose of the investigation is to learn more about the way the bacterium, Campylobacter, infects humans,so that we can ultimately take measures to prevent it. We would like your participation in our project.

Campylobacter is not a new disease nor is it an epidemic, it is only a newly recognized as we have just developed the technology to diagnose it from stool cultures. This illness often results in a severe diarrhea of several days duration. If you choose to participate in this study you will be interviewed in your home for about 45 minutes to one hour. You will be asked about your food preferences and food preparation, recent contact with other people and animals, recent travel, any recent illnesses, hobbies, and recent recreational activities. You will also be asked about your education and occupation.

Do you have any questions? Would you like to help us by participating in the study? When would be a good time for our interview?

_____

* We would also like to talk for 10 minutes either on the phone or in your home with other household members. We would like to ask them a few of the same questions we will ask you. Do you think that would be possible?

If any problem arises, please call and leave a message for _____ at the Communicable Diseases Division 625-2131.

DIRECTIONS:_____

_____

_____

_____

_____

Confirmation number and time:_____

*FOR FAMILY STUDY ONLY

We will be asking about what happened around the time of your illness so it may help you to remember if you mark the dates of your illness on a calendar as well as your activities in the week before your illness. Also, we don't know whether or not everyone who gets Campy, has diarrhea or whether or not everyone who is exposed gets it. For example, if 100 people were infected with it perhaps only 10 would be ill and 20 would have it in their stools. For this reason, we would also like to have stool samples from any other pets or people in your house who are willing to give us one, as well as any food samples you might suspect.

This portion of the study is voluntary as well, even if you should decide not to submit stools, we would still like to interview you.

If the samples are collected closer to the time of the illness and kept refrigerated, we are more likely to pickup the bug if it's there - if we wait until the interview, we might miss it. Therefore, we are asking people who are willing to collect their own samples. Would you like me to tell you how to collect the stools? You may use a newspaper underneath the toilet seat and then put the stool in a clean plastic butter dish or a jar with a lid, label the container with the date and name and put them in a paper bag in the refrigerator (they must be kept cold). Food samples should also be kept cold and covered.

I will pick them up at the interview or, if you prefer, they can be dropped off at one of our many drop off points. <u>Check which way they prefer to do it</u>.

Thank you so much - I am looking forward to meeting with you.

CASE CONSENT FORM

SEATTLE-KING COUNTY DEPARTMENT OF PUBLIC HEALTH

AND

GROUP HEALTH COOPERATIVE OF PUGET SOUND

CAMPYLOBACTER JEJUNI SURVEILLANCE PROJECT

Investigators: Charles M. Nolan, Director Communicable Disease Control, Seattle-King County Department of Public Health (206) 625-2131

Noreen Harris, Chief Project Epidemiologist, Communicable Disease Control, Seattle-King County Department of Public Health (206) 625-5909

Investigator's Statement:

PURPOSE AND BACKGROUND INFORMATION

The purpose of this research project is to gain information about infections due to a bacterium named Campylobacter jejuni. It has recently been discovered that this bacterium is an important cause of diarrheal illness in humans. As with any new illness there are many unanswered questions including where it comes from, how it is spread, and how to prevent it. This project has been undertaken to try to answer some fo these questions. The project has been approved by the Federal Food and Drug Administration.

You are being asked to participate because you were recently diagnosed as having an infection with Campylobacter or with a bacterium named Salmonella. Evidence of the infection was found in the stool culture taken at Group Health Cooperative during your recent illness. All persons treated by Group Health practitioners for Campylobacter infection are being asked to participate. Some persons treated by Group Health practitioners for Salmonella are also being asked to participate for comparison purposes.

If you decide to participate, an interviewer from the Seattle-King County Department of Public Health will interview you using a questionnaire designed to gather facts that could be helpful in determining how you become infected with Campylobacter or Salmonella. You will be asked questions about your household, recent trips you

have made, your pets, illnesses you and members of your household have had, activities you have been a part of, and types of food you have recently eaten, and background information such as age and occupation.

The interviewer will ask for your permission to obtain cultures from sites in your home that could help explain how you became infected with Campylobacter or Salmonella. These might include cultures from your kitchen, and leftover food. The cultures are done simply by swabbing the material with a dry or moistened but sterile swab. The interviewer might also ask for stool specimens from other members of your household and pets. If specimens cannot be given at this time, they will be given a container and asked to deliver them to the nearest point of pickup of the public health department transportation system. The kind of cultures and specimens that the interviewer requests will depend upon the answers to the questionnaire. This visit will take about one hour.

RISKS AND BENEFITS

We anticipate that no physical discomfort or risk will result from this visit. We also recognize that discussion of personal bowel habits and/or asking for a fecal specimen for culture may be distasteful to some individuals and may cause some psychological discomfort.

For those persons with Campylobacter infections, the immediate benefit of the project is that cultures taken in the home may provide information about the source of the infection. We believe that information from this project will help investigators formulate recommendations to the public and the medical profession about how to prevent Campylobacter infections

OTHER INFORMATION

The provision of services from the Seattle-King County Department of Public Health and Group Health Cooperative to which you are

entitled will be provided to you whether you participate in the study or not. Your decision to participate in this study is voluntary, and you may withdraw at any time. You may choose to not answer any quesion that you do not want to answer. You will not be compensated nor charged to participate in this study. You may ask questions about the procedures and the study at any time. If you have questions about your rights as a research subject, you may contact the Group Health Research Department at 326-6629.

The information we receive about you during the study will be identified by your name but only authorized members of the study will have access to this information. The information will be stored in a computer but all identifying information will be coded so that only authorized personnel will be able to access it. The information gathered in the study will be kept indefinitely so that it can be studied and analyzed. Your personal identity will not appear in any publication or presentation of the results of the study.

_____ _____
Signature of Investigator Date

Subject's Statement:

The study described above has been explained to me and I have had an opportunity to ask questions. I understand what will happen during the study, and that I have the right to withdraw at any time. I understand that personal information will not be identified in any publications. I voluntarily agree to participate and will receive a copy of this consent form for my records.

_____ _____
Signature Date

_____ _____
Guardian (if minor) Date

_____ _____
Interviewer Date

Copies: Subject
File

Mileage _____ Arrival Time _____ Departure Time _____

CAMPYLOBACTER / SALMONELLA STUDY

NAME: _____

ADDRESS: _____ _____ _____

HOME PHONE: _____ WORK PHONE: _____

1. Case/Control Number _____ (1=Case 2=Control) Index # _ _ _ 2. Interviewer: _____

3. Interview Date YY ____ MM ____ DD _____

4. Interviewee: Circle:
   1. Index person
   2. Spouse
   3. Mother
   4. Father
   5. Guardian
   6. Roommate
   7. Living-as-married
   8. Other* _____
   9. Don't Know

5. Interview Source: Circle:
   1. In-person (Home)
   2. In-person (Hospital)
   3. In-person other* specify _____
   4. Telephone
   9. Don't Know

CASES ONLY

6. Date first culture collected: YY MM DD

7. Source of first culture:
   1. Stool
   2. Rectal Swab
   3. Other (specify) _____
   9. Don't Know

8. When did _____ first feel ill: YY MM DD

8b. 2nd choice for onset: YY MM DD

9. When did _____ first feel well: YY MM DD

10. Were/Was ____ hospitalized for this illness?

Date Admitted	Date Discharged	Hospital Name

11. Frequency of diarrhea on worst day: Circle:
   0. No diarrhea during illness.
   1. Less than one episode every two hours
   2. At least one episode every two hours
   3. Did you loose control of bowels _____
   9. Don't Know

12. Presence of blood on worst day: Circle:
   1. None
   2. Specks and Streaks
   3. Abundant
   9. Don't Know

13. Highest fever: _____ Circle One: 1=Oral 2=Rectal 3=Arm
   1=< 100 2=100-100.9 3=101-101.9 4=Automatic 5=Skin 6=Guess
   4=102-102.9 5=> 103 6=fever, dk temp. 7=Didn't take or guess 9=Don't know

14. Which of the following signs and symptoms did ____ have?
   (At any time during the entire illness)

1=No
2=Yes
9=D.K.

Vomiting ____	Muscle Ache ____	Light sensitivity ____
Nausea ____	Weight Loss ____	Excess Gas ____
Abdominal Cramps ____	Dizzy ____	Other _____
Loss of appetite ____	Weak ____	
Chills ____	[illegible] present ____ (If antibiotic used, circle: clr	
Headache ____	[illegible] present before or after antibiotic)	
	[illegible] t Ache ____	

15. What antibiotics did _____ physician prescribe?
   0=None 1=Erythromycin 2=Tetracycline 3=Other* 9=Don't Know
   Brand if don't know _____

16. Antibiotics:

DATE BEGAN YY MM DD	DATE ENDED YY MM DD	NO. PER DAY	MEDICATION DOSE
			_____ UNITS
			250mg
			500mg

Was that how it was prescribed? _____

17. Did it help? (Circle) 1=No 2=Yes 9=Don't Know

18. Did ____ take anything to control diarrhea?

0=None 1=Lomotil 2=Other* 9=Don't Know

List if other _____

19. Antidiarrheal:

DATE BEGAN YY MM DD	DATE ENDED YY MM DD	NO. PER DAY	MEDICATION DOSE
			_____ UNITS

20. Did it help? (Circle) 1=No 2=Yes 9=Don't Know

EVERYONE

FOR QUESTION 21 USE THE FOLLOWING CODE:

0=Never 3=3 Times 6=6 times 7=greater than 6
1=Once 4=4 Times 9=Don't Know
2=Twice 5=5 Times

(PG visits note separately)

21. How often in the last year, that would be one year from today, did you see a nurse, physician, or madex for wellness, not illness or injury - such as a physical, vaccination, pap smear, or some preventative care._____

22. Was/Were _____ ill in any of the 7 days before

1=No 2=Yes*, GI Only 3=Yes*, non-GI 9=Don't Know

*If yes, specify: symptoms _____

Date Onset YY MM DD	Date Ceased YY MM DD
_____	_____
_____	_____

24. Did_____ have any chronic illnesses for which_____ are being treated by a physician: 1=No 2=Yes* 3=D.K.

*If yes, specify illnesses and medications_____

_____

25. Were/Was _____ taking antibiotics in any of the 7 days before:

1=No 2=Yes* 9=Don't Know

*If yes, list antibiotics: _____

_____

26. Were/Was _____ taking vitamins or supplements in any of the 7 days before: (Suggest brewers yeast, minerals)

1=No 2=Natural or Organic 3=Regular 4=Yes, don't know kind
5=Yes, both 9= Don't Know

27. Number residing in your home other than index name _____

(Go back 1 week before index date to now)
Beginning with the youngest, please list:

ID	Name	Sex	Age	Relationship	Duration In Household	Country Of Origin
Same as HSF if sample taken		1=M 2=Fe		1=Spouse/2=Parent 3=Child/4=Sibling 5=Partner 6=Other relative* 7=Other non-relative* 8=Housemate 9=D.K.	1=<three mo. 2=>three mo.	1=U.S. 2=Other* specify 9=D.K.

28. Did any household members other than _____ have any illness within the 7 days before:

1=No 2-yes* 9=Don't Know

*If yes, complete

NAME	Symptoms If G.I.	Date of Onset YY	MM	DD	Date Ceased YY	MM	DD	Culture Taken	Results
								1=No 2=Yes 3=Yes,GHC 4=Yes,other* 5=requested, not submitted	0=Negative 1=Campy 2=Other 9=D.K.

29. Did any household member other than ____ have any illness
CASE HOME: in any of the 7 days before or anytime since onset:
CONTROL HOME: in any of the 21 days before this interview.

If yes, complete: 1=No 2=Yes 9=Don't Know

NAME	Symptoms If G.I.	Date Of Onset YY	MM	DD	Date Ceased YY	MM	DD	Culture Taken	Results
								1=No 2=Yes 3=Yes, GHC 4=Yes,other* 5=requested, not submitted	0=Negative 1=Campy 2=Other 9=D.K.

30. Were/Was _____ in contact with anyone outside of your home who had illness within the 7 days before or after (CASES) / 21 days before (CONTROLS) that you were aware of?

1=No 2=Yes* 9=Don't Know

*If yes, complete and indicate date and place of contact: _____

Name/Symptoms if G.I.	Age Yrs.	Sex 1=M 2=Fe	Relationship 1=Relative, include step or in-law 2=Friend 3=Co-worker 4=Teacher or Caretaker 5=Boy/Girl Friend 7=Adults cared for 8=Other 9=D.K.	Date of Onset YY	MM	DD	Date Ceased YY	MM	DD	Culuture Taken 1=No 2=Yes, us 3=Yes, GHC 4=Yes, other 5=Requested, not submitted 9=D.K.	Result 1=Campy 2=Other 9=D.K. 0=Neg.

31. Were/Was _____ in contact with any animals or birds in the 7 days before: (Suggest pets, strays, wild, farm, zoo, fish turtles, hamsters, gerbils

1=No 2=Yes 9=Don't Know

Type & ID	AGE 1=≤6 months 2=≥6 months 3= don't know	1=shared house 2=on premises 3=elsewhere 9=don't know	Frequency Of Contact 1=daily 9=D.K. 2=weekly 3=monthly 4=a couple of times 5=once/6=No touch

32. Did any of the animals have any illness in any of the
CASE: 7 days before or after
CONTROL: 21 days before

1=No 2=Yes 9=Don't Know

If yes and GI	Animal(ID)	Dates	Symptoms if GI

33. Did any of the animals sleep on ____ bed in any of the 7 days before:

1=No 2=Yes* 9=Don't Know

*If yes, indicate which animal _____

34. Did _____ feed any animals or handle the food of any of the animals in any of the 7 days before:

1=No 2-Yes* 9=Don't Know

*If yes, indicate which animal _____

35. Did ____ clean up animal feces, change a litter box, or in any way come into contact with the feces of animals in the 7 days (i.e. any manure or feces in yard or garden).

1=No 2=Yes 9=Don't Know

*If yes, indicate which animal _____

36. Were any of the animals new (known for less than 1 month) to _____?

1=No 2=Yes* 9=Don't Know

*If yes, indicate which animal and how new _____

37. Which of the following do you feed your pets or animals in the 7 days before:

1=No 2=Yes 9=Don't Know

Cooked Table Scraps _____

Commercially Prepared Food _____ Brands _____

Raw animal products including raw milk, raw meat, poultry, bones or eggs _____ which _____

Do your animals hunt or scavenge? _____

Drink from toilet bowl or drink untreated water outside? _____

38. Did _____ travel more than thirty miles from your home (either in-state, out-of-state, or out of the U.S.) in the 7 days before (excluding regular commuting)

1=No 2=Yes* 9=Don't Know

*If yes, specify when, where, and means of travel:

Date YY	MM	DD	Destination	Means of Travel 1=No 2=Yes 9=Don't Know Car	Bus	Train	Airplane	Ship	D.K.

39. Did _____ participate in any outdoor activities (i.e., skiing - alpine or x-country; sledding; trail riding - horses or bikes; pack trip; hiking; backpacking; camping; mountaineering; spelunking; playing in sand; picnic in woods or remote area; chopping wood in forest; etc.) during any of the 7 days before

1=No 2=Yes* 9=Don't Know

*If yes, complete

Activity	Date YY	MM	DD	Location

40. Outside of your own home did ____ drink any water from any of the following sources, including drinking fountains supplied by these sources, in the 7 days before:

1=No 2=Yes* 9=Don't Know

*If yes, specify:	Code	Date YY	MM	DD	Location
Private Well					
Stream, Creek, or River					
Lake					
Pond					
Bottled					
Snow					
While on trip, ice, brush teeth, tap water					

If Yes, did you attempt to treat the water in any way? specify:

41. What was the source of your home water supply in the 7 days before: (residence only)

1=City Water Plant
2=Community Well
Circle: 3=Semi-Public Well
4=Private Well
5=Surface water
6=Spring
9=Don't Know

42. Is it disinfected or filtered in any way?

1=No 2=Yes 9=Don't Know

43. To whom do you pay your water bill? _____

43a. Do you rent or own? 1=own 2=rent 3=living rent free 9=D.K.

44. Did _____ play, water ski, fish or swim in any of the following during any of the 7 days before:

1=No 2=Yes* 9=Don't Know

*If yes, complete

		1=Private 2=Public	DATE YY MM DD	LOCATION
Circle:	Jacuzzi, whirlpool, hot tub sauna (wet or dry)			
Circle:	Ocean or Puget Sound			
	Hot Springs			
Circle:	Pool, regular or wading			
Circle:	Lake, river, stream or creek			
Circle:	Shower with untreated water (Out of U.S. OR rural motel)			

45. What type of sewage treatment do you have for your home?

1=Municipal Sewage
2=Septic Tank
3=Cesspool
4=Chemical Toilet
5=Other*
9=Don't Know

45a. Sewage treatment on trip: _____ (Same options as #45).

46. Has your plumbing or sewage backed up in the 7 days before?

1=No 2=Yes 9=D.K.

46a. Sewage problems on trip? _____

In the 7 before, any contact with sewage or toilet water (if toddler, did they put any in their mouth or play with it and put their hands in their mouth?)

1=No 2=Yes, sewage contact 3=Yes, toilet water contact 4=Yes, in mouth 9=D.K.

47. In any of the 7 days before were/was _____ in contact with a child under 5 who attended daycare, nursery school or a group babysitting situation?

1=No 2=Yes* 9=Don't Know

Name of Child Attending (Note relationship to index)	Age	Sex	Name of Daycare	Location

NOT FOR CHILDREN UNDER 10:

48. Did_____smoke cigarettes in any of the 7 days before:

1=No 2=Yes 9=Don't Know _____

49. Did_____smoke marijuana in any of the 7 days before:

1=No 2-Yes 9=Don't Know _____

DEMOGRAPHIC QUESTIONS

50. Birthdate YY MM DD

51. Race(Circle) 1=White 2=Black 3=Asian 4=Indian 5=Chicano
6=Other* 9=Don't Know

52. Occupation in the 7 days before (see Occupational Code Sheet- if child under 17 please note both parent's occupation and child's employment.)

Case/Control _____
Mother _____
Father _____
Spouse _____
Guardian or Step-parent _____

53. If there was a second occupation or volunteer work in the 7 days before.

Case/Control _____
Mother _____
Father _____
Spouse _____
Guardian or Step-parent _____

53.a. Index Sex: 1=Male 2=Female

54. Did ___have any hobby which you engaged in during the 7 days before:

Case/Control _____
Mother _____
Father _____
Spouse _____
Guardian or Step-parent _____

55. Marital Status: 1=Married 2=Never married 3=Divorced/Separated
(Circle) 4=Widowed 5=Living-as-married 9=Don't Know
Note: If ≤ high school age, record parents' status

56. How many bathrooms are there in your residence? _____

57. Census Tract: _____ / Density _____ Location _____

58. Number of years of education completed (if child under 17 indicate years of education completed by parents as well) exclude kindergarten

1= Grades 1-6
2= Grades 7-8
3= Grades 9-11
4= Grade 12
5= Trade School
6= 1-3 yrs. college
7= College graduate
8= Post-college Graduate
9= Don't Know

Case/Control _____
Mother _____
Father _____
Spouse _____
Guardian or Step-parent _____

59. On what surface(s) do you prepare or cut your cheese, bread, vegetables and already cooked foods?

IN 7 BEFORE _____ (porous/smooth)

USUALLY _____ (porous/smooth)

On what surface(s) do you prepare or cut your raw meat, poultry, or fish?

_____ (porous/smooth) (different/same/D.K.)

_____ (porous/smooth) (different/same/D.K.)

60. What method do you use to clean cutting board or food preparation surface?

	7 before	usually	7 before	usually	7 before	usually
meat & veggies	_____	_____	_____	_____	_____	_____
meat only	_____	_____	_____	_____	_____	_____
veggies only	_____	_____	_____	_____	_____	_____
	1=wipe 2=rinse 3=dishwasher		1=warm 2=hot		1=none 2=soap or detergent	

61. How often do you clean that cutting board or food preparation surface?

Circle: 1=Once Per Week
2=Once Per Day
3=After every Meal
4=In-between each food item
9=Don't Know

62. Do you have a vegetable garden that you would have used in the week before:

1=No 2=Yes* 9=Don't Know _____

63. *If yes, do you use any of the following? 1=No 2=Yes 9=Don't Know
Manure _____ Commercial Dry Fertilizer _____ Other _____
Note: If handled manure or fecal contaminated garden in 7 days before, indicate in question 35.

64. If yes, do any domestic animals defecate in your garden?

1=No 2=Yes* 9=Don't Know _____

*If yes, specify which animals:

Type	Age	Sex

65. During the 7 days before, did ____ eat food prepared by or prepared in any places other than your own home? (Suggest fast food restaurants, restaurants, someone else's home, picnic, social gathering, cafeteria, camp stove, open fire.)

1=No 2=Yes* 9=Don't Know _____

NAME	LOCATION		DATE YY	MM	DD

FOOD QUESTIONNAIRE FOR INFANTS LESS THAN 18 MONTHS

66. Did you use any of the following for preparing your child's food or as a source of milk in the 7 days before? 1=No 2=Yes 9=Don't Know

	Used in 7 days before.	Brand & Type
Your own breast milk		
Whole milk		
2% milk		
Raw milk		
Condensed Milk/Evaporated		
Powdered Milk		
Milk Substitute (Soy bean milk), include formula		
Acidofillus milk		
Surrogate mother's milk		
Goat's Milk-raw		
Goat's Milk pasteurized		

67. Did your infant eat the following foods in the 7 days before?

	Used in 7 days before	Brand & Type
Food Home-prepared formula-from scratch		
Commercially Prepared formula (similac, etc.)		
Commercially prepared meat containing baby foods		
Commercially prepared veg. containing baby foods		
Commercially prepared fruit baby food		
Commercially prepared baby fobd desserts		
Vitamin Supplements		
Health foods such as tofu, Kimchee, etc. or others		
Some of the same food you serve the rest of the family *		

*If yes, administer the full food preference questionnaire.

Anything else not mentioned._____

68. Eat or taste anywhere any- DAIRY PRODUCTS (such as) CIRCLE	IN 7 DAYS BEFORE? 1=No 2=Yes 9=D.K.	ITEM...BRAND/ WHERE PURCHASED
PASTEURIZED MILK: choc.,skim,lowfat, 2%, powdered (either by itself or in hot drinks)		
MILK BEVERAGES: cocoa,shakes,malts		
YOGURT		
MILK DESSERTS: ice cream,ice milk,sherbert, and puddings		
CREAM: ½&½, sour, real whipping		
RAW MILK PRODUCTS : butter,cream,ice cream, milk, and yogurt		
SOFT CHEESE: cottage,farmers,ricotta,cream, neufchatel		
HARD CHEESE: cheddar,havarti,parmesan, monterey,swiss,gouda,edam,mozzarella,blue		circle if natural
CREAMY DIPS,SAUCES,AND SALAD DRESSINGS: chip and vegetable dips, creamy cucumber, hollandaise,bernaise,cheese sauces,Roquefort		
CREAM SOUPS: mushroom, celery oyster, chowders, bisque		
COOKED EGGS: boiled-soft, med.,hard, scrambled-soft,med.,hard, fried- sunny side, over easy, hadr, souffles, timbales, omelets, french toast, crepes		
POWDERED EGGS		
RAW EGGS: in nogs, caesar salads, julius, smoothies, mixed drinks, meringue, steak tartar		
PANCAKE AND DESSERT MIXES		
TOFU,KIMCHEE, TEMPEE		
GLAZED, FROSTED, OR ICED DESSERTS: donuts,cakes,pies,cookies,and rolls		
CREAM FILLED DESSERTS: eclairs,pies, rolls		

Eat or taste anywhere any:

FRESH (RAW) MEAT meaning purchased raw (including frozen) and restaurant food CIRCLE	IN 7 DAYS BEFORE 1=No 2=Yes 9=D.K.	ITEM... BRAND/WHERE PURCHASED
FRESH PORK: uncured ham, sausage, chops, roast (also in pies, stew, soups, casseroles, Chinese, and other ethnic dishes)		
FRESH BEEF: hamburgers, steaks, liver, roast, veal (also in pies, stew, soup, casseroles, chili, Mexican, Italian, Chinese, and other ethnic dishes)		
FRESH LAMB OR MUTTON (also in pies, casseroles, soups, or casseroles)		
FRESH TURKEY: roasts, parts (also in pies, casseroles, soups, and stews)		
FRESH CHICKEN: broiler, fryer, baked (also in pies, casseroles, soups, Mexican, Chinese, and other ethnic dishes)		
FRESH FISH: salmon, cod, halibut, perch, sushi, sashimi, caviar (also in boullabaisse, cioppini, casseroles, salads, Chinese, and other ethnic dishes)		
FRESH SHELLFISH: clams, oysters, abalone, geoduck, mussels, crab, lobster, scampi, crayfish, shrimp, scallops (also in soups, casseroles, salads, sandwiches, Chinese & other ethnic dishes		
WILD GAME OR OTHER MEATS: deer, bear, squirrel, raccoon, rabbit, horse, goat		Domestic/Wild
WILD FOWL AND OTHER POULTRY: pheasant, quail, duck, geese, ~~etc.~~ Cornish game hen		Domestic/Wild

Eat or taste anywhere any:

PROCESSED FOODS (canned, frozen, dehydrated, pre-packaged dinners, cured, smoked, already cooked, T.V. Dinners)

CIRCLE	IN 7 DAYS BEFORE 1=No 2=Yes 9=D.K.	ITEM...BRAND/WHERE PURCHASED
PORK: sausage, cured ham, sandwich meat, hot dogs, spam, bacon (also pork & beans, casseroles, T.V. dinners, frozen, pre-packaged dinners)		
BEEF: liverwurst, salami, pastrami, luncheon meat, jerky, hot dogs, bologna, corned (also in pot pies, T.V. dinners, frozen, pre-packaged dinners, lasagna, Mexican dishes, Chinese and other ethnic dishes)		
TURKEY: roll, sandwich meat, hot dogs, pot pies, bologna, T.V. dinners, etc.		
CHICKEN: roll, sandwich meat, hot dogs, pot pies, bologna, T.V. dinner, frozen, pre-packaged dinners		
FISH: tuna, smoked salmon, sticks, smoked halibut, kippers, herring, sardines, anchovies, T.V. dinners, frozen, pre-packaged dinners		
SHELLFISH: scampi, oysters, crab, scallops, abalone, clams, mussels, geoducks, lobster, shrimp (cans, T.V. frozen dinners, pre-packaged, etc.)		

Eat or taste anywhere any: VEGETABLES CIRCLE	IN 7 DAYS BEFORE 1=No 2=Yes 9=D.K.	HOW EATEN? 1=Raw 2=Fully cooked (steam, stir fry, saute) 9=D.K.
FRESH SPROUTS, LETTUCE, SPINACH, CELERY, WATERCRESS, CABBAGE		
FRESH CUCUMBERS, ZUCCHINI, CARROTS		
FRESH LEEKS, GREEN ONIONS, ONIONS		
POTATOES, TURNIPS, RUTABAGAS		Raw w/skins Cooked w/skins
FRESH BRUSSEL SPROUTS, BROCCOLI, CAULIFLOWER		
FRESH BEANS, GREEN, LIMA, STRING, SOY BEANS, ETC.		
MUSHROOMS		
ANYTHING ELSE REGULARLY EATEN NOT MENTIONED		

69. Did _____ taste or eat any health foods or organically grown foods in the week before?

1=No 2=Yes* 9=Don't Know

*If yes,

ITEMS	BRAND	DATE YY MM DD	WHERE BOUGHT

70. While preparing meals or at any other time in the week before did _____ taste or eat any raw, very rare, or partially cooked meat, poultry, or fish?

1=No 2=Yes* 9=Don't Know

ITEMS	DATE YY MM DD	BRAND/WHERE BOUGHT

71. Did _____ taste or eat any unpeeled raw vegetables or fruit in the week before?

1=No 2=Yes* 9=Don't Know

Were they: 0=unwashed 1=rinsed 2-washed with soap and water 9=D.K.

ITEM	WHERE BOUGHT

72. In the 7 days before did _____ taste or try any new foods or brands that _____ doesn't regularly eat? (anything unusual, even if regularly eaten e.g. pica, snow)

1=No 2=Yes 9=Don't Know

FOOD	DATE YY MM DD	BRAND/WHERE BOUGHT	Where prepared	How prepared

73. In the 7 days before, did you buy food at:
1=No 2=Yes 9=D.K.
Supermarket _____
Local grocery store or deli_____
Fast Food Mart _____
Health food store or counter _____
Open market _____
Roadside stand _____
Coops _____

Name of Store	Location

74. What do you think caused the illness?

75. Where any of the questions confusing? 1=No 2=Yes _____

76. Were any of the questions offensive? 1=No 2=Yes _____

POSITIVE EXPOSURES

Question # / Exposure	Other Close contacts who were exposed or comments
24 Chronic illness	
25 Antibiotics	
26 Vitamins-suppl.	
30 Human Contact w/GI	
31 Animal Contacts	
35 Animal Feces	
38 Travel	
39 Outdoor Activities	
40 Outside Water	
44 Swim	
47 Daycare	
49 Marijuana	

52,53,54 Occupation

65 Eating Out

68 Suspect Foods
Infant's formula/milk etc.
Infant's food

Dairy products

Fresh meat/fish/fowl

Processed foods

Fresh Vegetables

70 Taste while preparing

71 Taste unpeeled raw veggies

72 New foods

Cln	0	1	2	3	4
SES	I	II	III	IV	V
Hlth War	0	1	2	3	4
Comply	0	1	2	3	4
Reliab	0	1	2	3	4

SRC 1_____
2_____
3_____
4_____
5_____

INSTRUCTIONS FOR STOOL SPECIMEN COLLECTION

1. Put newspaper under toilet seat creating an upside down "hat" or use "hat" given to you by the Health Department.
2. Collect the stool as soon as possible.
3. Collect roughly a tablespoon.
4. Place amount in Health Department cup or in clean dry screw top jar.
5. Label specimen with name, date, and CD - Dr. Harris.
6. Keep refrigerated and transport to Health Department in clean dry paper bag.
7. Make sure there are no leaks in the jar or the bag.
8. Label the bag with the label provided by the interviewer.
9. Request that the sample be immediately refrigerated when dropped off.
10. Place household sampling form in the bag with the samples if such a form was provided.

RECTAL SWAB PROCEDURE

Make sure tube is labeled: C.D., your name, the date and Dr. Harris.

1. Remove paper wrapper (read instructions on wrapper).
2. Insert swab into test tube and moisten swab in tube.
3. Remove swab from test tube. Carefully insert swab into anus until feces stains swab.
4. Remove swab and re-insert into test tube.
5. Break off portion of stick protruding from the tube so that cap can be screwed down tight on test tube.
6. Make sure there are no leaks.
7. Keep refrigerated.
8. Label the bag or a box with the label provided by the interviewer.
9. Request that the sample be immediately refrigerated when dropped off.
10. Place household sampling form in the box with the samples if such a form was provided.

APPENDIX B

AN OUTBREAK OF *C. jejuni* INFECTION ASSOCIATED WITH A COMMERCIAL RAW GOAT'S MILK DAIRY

An Outbreak of Campylobacteriosis Associated with a Commercial Raw Goats' Milk Dairy

Six cases of enteritis caused by *C. jejuni*, associated with a commerical raw goat milk dairy, in July and August of 1983, were recognized as a result of the case surveillance system conducted as a part of the present study, (FDA Contract # 223-81-7041). This outbreak investigation contributes the following new information: the identification of raw goat milk as a source of human *C. jejuni* infection; the prevalence of *C. jejuni* in three commercial goat dairies; and demonstration of the usefulness of some of the phenotypic characteristics of *C. jejuni* as epidemiologic markers.

Methods and Results

Two cases of laboratory-confirmed *C. jejuni* infection in raw goat milk drinkers occurring within three days of each other aroused the interest of the Seattle-King County Campylobacter Project's epidemiologists. The index case, a single thirty-year old window washer, was reported to the Health Department's Communicable Disease Division by the patient's physician, a practice not required but encouraged by the Seattle-King County Health Department. The second case was a 6 month old infant, whose mother was interviewed as part of Project's case-control study. In order to augment the case surveillance in the GHC population, a decision was made to institute active county-wide surveillance in mid-August 1983, after the first two cases in milk drinkers

were recognized. All sixteen clinical laboratories aside from GHC located in King County were contacted. Fifty-eight of eighty-two patients (70.7%) with C. jejuni infection, confirmed by culture between July 15 and August 15, were interviewed by phone regarding the onset of symptoms, ill family members, and the dairy products they had consumed in the week prior to their onset.

Additionally, all GHC case-control interviews conducted in the previous 16.5 months as part of this project were reviewed for exposure to goat milk. None of 173 cases and two of 464 (0.4%) controls responded affirmatively to the question confirming our suspicion that such an exposure was indeed rare.

When the GHC patients were included, a total of 102 cases had been diagnosed in the county between mid-July through mid-August, 1983. The six cases who either drank milk or were affiliated with the dairy began their illnesses between July 15 and August 3, 1983; thus, these dates defined the "outbreak period." Forty-two cases were ineligible either due to their residency or because their illness occurred outside of the outbreak period. Twenty patients were lost to follow-up, and three were excluded as they couldn't determine when their illness began.

Two case-control studies were instituted the third week in July, both of which included all 37 identified culture-confirmed cases who resided in King County and whose onsets occurred in the four weeks beginning July 15.

Family Study

Appendix B-2

The first, a family study, included all family members from each of 35 case households (only households with at least two members). A case-definition which included any symptoms of enteritis was used to identify the potential C. jejuni cases within the case households during the outbreak period. Seven additional family members with enteritis were identified, one of whom was culture positive.

A condensed version of the Project's main questionnaire was administered by phone, and family members were queried as to their exposure to specific dairy products, foods, and animals as well as any history of gastro-intestinal illness.

Two of the Project's regular interviewers conducted all of the interviews for the outbreak investigation. The risk of C. jejuni infection with an exposure relative to the risk in those who were not exposed, i.e., the relative risk, was estimated according to the method of Mantel and Haenzel. 95% confidence intervals were calculated as well. The risk factor analysis was summarized after stratifying by household using a FORTRAN computer program.

Population Controls

The second study design, an age and sex-matched case-control study, utilized the same reported 37 cases but included population controls. These controls were selected from two groups depending on whether or not the case was a member of Group Health Cooperative.

Matched controls were selected for the GHC cases from the pool of previously interviewed GHC controls who had been systematically selected from the GHC membership register. A match was selected who was the same sex and in the same age group (age groupings were less than 1, 1-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40-49, 50-59, over 60) as the case and whose interview date was as close the case's date of onset as possible. All but three population controls were interviewed within two weeks of the onset of symptoms in their matched case. The three exceptions were interviewed within two months of their cases. All GHC interviews were conducted in the home.

For the 25 non-GHC cases occurring in the outbreak period, controls were selected by repeatedly adding one digit to the case's residential phone number and dialing until a match was found who was the same sex and in the same age group as the case. The non-GHC case and control interviews were conducted over the phone. In both outbreak studies, one interviewer was responsible for interviewing each case and his/her family as well as the population controls.

Relative risks and 95% confidence intervals were determined in the same fashion as for the family study.

Dairy Survey

The implicated dairy (Dairy A) and two other commerical raw goat milk dairies located around Puget Sound (Dairy B and C) were sampled. The estimated herd sizes for Dairy A and C were approximately 100 goats. Both dairy A and B were closed dairies, which

bred their own stock. Dairy A, however, imported milk from another goat herd. Dairy A was experiencing a relatively high prevalence of mastitis (roughly 25% of the milkers), whereas only one goat was reported with mastitis in Dairy B and none in Dairy C. Dairy B with only 70 goats was the smallest herd and the only one which imported stock.

All three dairies used automatic milking machines, washing the udder before and after milking with an iodine preparation. The herds are monitored annually for TB and Brucellosis. Monthly, one sample of each of the dairy's products is taken and tested for total leucocytes, bacterias, and coliforms. All tests fell within normal limits for all three herds. In May, all were tested; in August, Dairy A and B; and Dairy B was tested in July as well.

Twenty-five milkers, four kids, one ram and one farm dog were sampled, ten goats from each dairy. The six fecal samples were taken rectally. The remaining samples were rectal swabs which were transported in Cary-Blair medium. Three milk and one yogurt sample from Dairy A were tested both by the FDA and the Seattle-King County Health Department. The owner of Dairy A refused permission to interview and/or sample any of its staff or family.

Laboratory Tests

Isolates from all but one GHC case (non-viable), all but one of the identified goat-associated cases, and those cultured from

the goats were confirmed as C. jejuni by the Seattle-King County Health Department. All isolates were subjected to antibiotic susceptibility testing, plasmid analysis and serotyping by the Lior and Penner techniques as described in the Methods Section of this report.

Results

The cases ranged in age from 6 months to 71 years. The illness was characterized by diarrhea (100%), fever, cramps, muscle ache, weight loss, weakness, flatulence (83.3%), headache (66.7%), nausea and dizziness (50%), loss of appetite (33.3%) and vomiting and photophobia (16.7%).

Four of 38 culture-confirmed cases (10.5%) occurring in the outbreak period drank Dairy A's goat milk in the week prior to their illness. Two of the cases denied consuming the milk. One was employed as an office worker by the dairy (see figure 1), and the second, her infant son, was recovering from open heart surgery. He had been given the milk several months prior to his illness and had eaten some of the dairy's pasteurized yogurt in the week before his symptoms. Both the mother and son had camped with the dairy's owner's family approximately two weeks before the mother developed diarrhea. During the camping trip, two of the owner's children were experiencing severe diarrhea. The mother also reported using goat manure on the family vegetable garden. In the same household, the father and two other children, who were not ill, had no contact with the dairy, did not eat any of the products, and were culture negative.

Ten of the 45 Campylobacter-like and cu..ure-confirmed cases occurred in the family contacts of eight cases (see figure 1). Secondary transmission is likely in all but one of the households, based on timing of the illnesses, but can't be confirmed as in all of the households the source was unknown.

For the matched study, the Group Health subjects and non-Group Health subjects from King County did not differ with regard to the exposures of interest. Thus, they were combined during the analysis.

Exposure in the week prior to onset/interview to cow's milk, raw eggs, raw or cooked chicken, raw or rare beef, all contacts, puppies or kittens did not appear to play a role in the etiology of the cases occurring during this period (see table 1).

Consumption of the implicated brand of raw goat milk and/or contact with the dairy were associated with large relative risks in both the family and matched studies. In the latter study, however, as none of the controls were exposed, the point estimate for the relative risk in each case was infinity. The test-based confidence limits were inestimable ($p \leq 0.05$) occurrences. In the family study, there was a 95% probability several hundred times as many cases as controls drank the implicated brand ($p=0.02$).

More than three times as many cases as controls drank untreated water in the week prior to onset/interview, but this difference was only statistically significant for the matched study using non-family controls.

Finally, all family members were 9.5 times as likely to have

43-016 O - 85 - 43

reported animal contact in the week prior to illness, interview non-ill family members (p=0.05). This did not hold true for outside controls, as they were twice as likely to have animal contacts as their case-matches.

Laboratory Tests

As can be seen in Table 2, the outbreak strain was hippurate positive, sensitive to all antibiotics except sulfasoxzole-trimethprin; negative for plasmids, Lior serotype 36, and reacted to antibodies for Penner antigens for 3, 4, and 13. Reactions to Penner 6 and 25 occurred in some of the strains.

Table 3 illustrates the findings from the dairies. Dairies A and B had three positive goats each as contrasted with none in C (P=0.10) (Fischer's exact for 2X2 table). In Dairy A, three of the milkers were positive, one of whom was mastitic. In Dairy B, one of seven milkers was positive, and two of two kids were positive. The six fecal samples taken were all from Dairy C.

Two of the positive goats from Dairy A appeared to be infected with the outbreak strain including one with mastitis. The remaining goat was carrying an organism which was not typeable by Lior, contained Penner 6, 25, and 44, and was sensitive to all antibiotics.

The three isolates from Dairy B differed from the outbreak strain as they were hippurate positive, multiply resistant strains which contained plasmids, and serotypes 4 and 14. All attempts to isoalte C. jejuni from the milk and yogurt were

unsuccessful.

Discussion and Conclusion

This outbreak demonstrates the potential for unpasteurized goats' milk like raw cow's milk to serve as a source of human C. jejuni infection. The evidence incriminating Dairy A in this outbreak includes the phenotypic characterization of the organism in combination with the risk factor analysis. The presence of the outbreak strain only in Dairy A supports the dairy's milk as the source of the outbreak as well. In addition, Dairy A alone was observed to be experiencing a high level of mastitis, which is known to be caused by C.jejuni in dairy cattle. The organism has also been observed in dairy cattle in the absence of recognized human infections, as in Dairy B. The study, which used population controls, is certainly open to challenge as control selection and interviewing of the Group Health Cooperative subjects differed from the methods used to select and conduct interviews with county subjects. The main difference was that GHC subjects were interviewed at home using the main questionnaire, whereas the county cases were interviewed on the telephone at the time of outbreak. Insufficient resources did not permit home interviews for county cases, nor would GHC permit recontacting their previously interviewed subjects for repeat phone interviews. Secondly, the GHC controls were not matched on neighborhood, whereas the county controls were. Again, we were not able to re-interview controls for GHC cases and the neighborhood match for county cases was used mainly to motivate county residents to

participate, without previous introduction, as well as to provide a selection tool. In order to determine what effect, if any, these differing approaches had on the results, the analysis was first handled separately for both groups. The results of the family study, which was conducted over the phone for all households, was consistent with the results of the population study suggesting neighborhood did not confoun the results.

Finally, as most C. jejuni cases do not appear to be linked, characterization of the organism by plasmid analysis, hippurate hydrolysis (which although not 100% reliable can be used to differentiate C. coli (-) and C. jejuni (+)), and Lior serotyping may be initial tools necessary to elucidate the epidemiology of this organism and identify outbreaks. For this outbreak the single most useful marker was the Lior serotype.

FIGURE 1

EPIDEMIC CURVE: GOAT MILK OUTBREAK

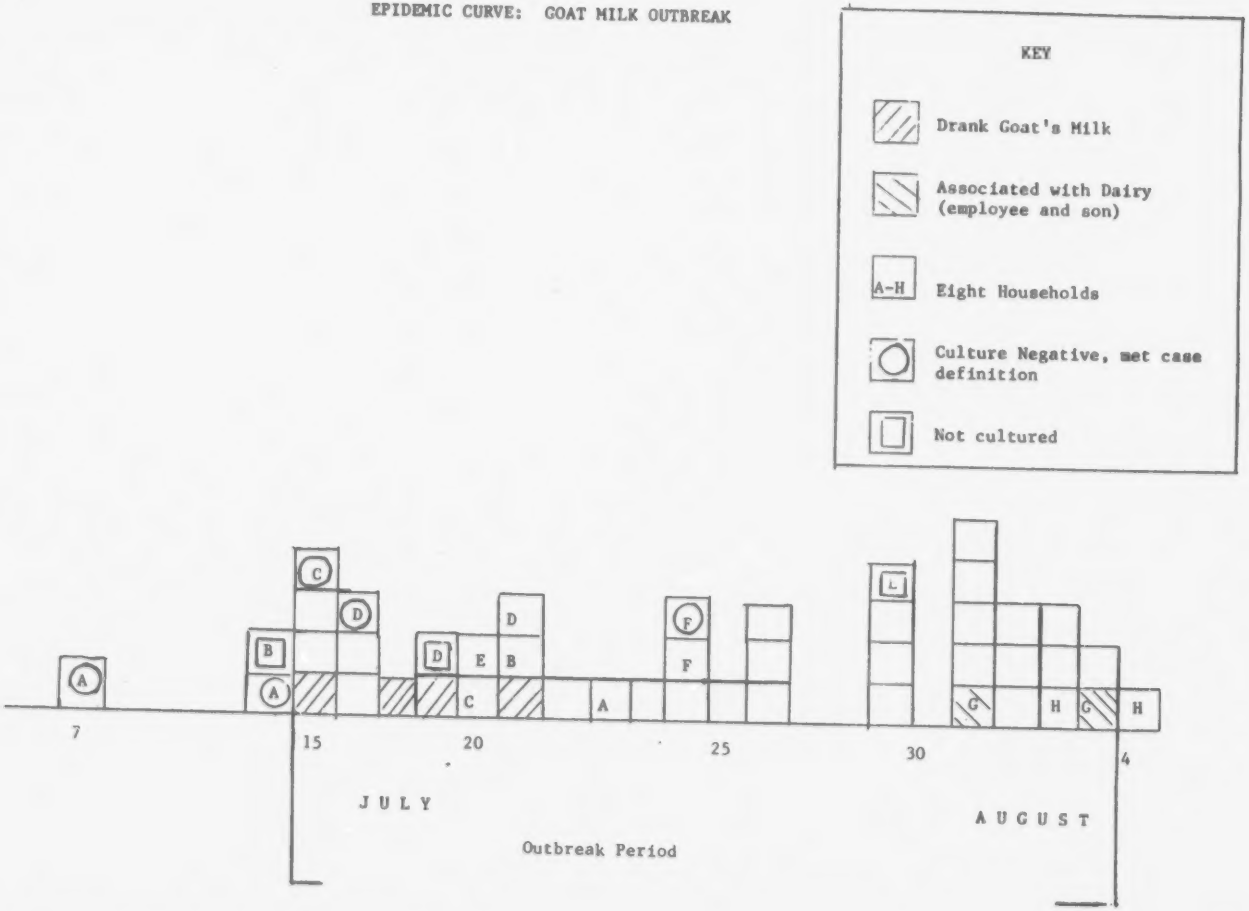

Table 1: Matched Controls

Exposure	Outside Controls Combined			Family Controls		
	Relative Risk	(95% CI)	Two-tailed P-value	Relative Risk	(95% CI)	Two-tailed P-value
Cow's milk	.50	(.18-1.43)	.20	.57	(.20-1.64)	.29
Raw goat's milk	∞	(—)	.05	1.47×10^5	($430-4.97 \times 10^7$)	.02
Raw eggs	5.0	(.72-34.51)	.10	3.12	(.56-17.42)	.19
Animal contacts	.50	(.13-1.95)	.32	9.53	(.97-93.58)	.05
Chicken (cooked or raw)	1.33	(.46-3.83)	.59	1.01	(.32-3.13)	.99
Beef (cooked or raw)	1.0	(1.0-1.0)	—	1.50	(.06-39.73)	.81
Raw water	3.33	(.99-11.24)	.05	3.07	(.39-24.40)	.29
Ill contacts	3.0	(.35-25.84)	.32	0.0	(—)	.48
Ice cream	1.0	(1.0-1.0)	—	∞	(—)	.32
Yogurt	1.0	(1.0-1.0)	—	∞	(—)	.32
Raw or rare chicken vs. not eaten	∞	(—)	.32	—		—
Raw or rare meat vs. not eaten	—		—	—		—
Raw or rare chicken vs. cooked or none	1.0	(1.0-1.0)	—	—		—
Raw or rare meat vs. cooked or none	1.0	(1.0-1.0)	—	—		—
Dairy association	∞		.01	2.80×10^5	(4.6×10^3-1.68×10^7)	.001
Raw goat's milk + goat yogurt	∞		.03	2.13×10^5	($522-8.7 \times 10^7$)	.01
Goat yogurt	—		—	—		—
Puppy contact	.60	(.15-2.47)	.48	—		—
Kitten contact	.75	(.17-3.33)	.71	2.33	(.06-95.65)	.65

Table 2

Source of Sample	Date Onset	Antibiogram (R, S, I) ERY	TET	STP	AMP	SXT	Hippurate	Plasmid Profile	Serotype Penner	Lior
Patient 1 7	7/20	S	S	S	S	R	+	---	3,13w,4w(6)	36
Patient 2 (index)	7/15	S	S	S	S	R	+	---	13,4w(25)(3)	36
*Patient 3 (1st Blood)	7/31	S	S	S	S	I	+	---	3,13w,14w(6)	36
(2nd Blood)		S	R	S	S	R	+	---	13,4w(25,6)(3)	36
(Stool)		S	S	S	S	R	+	---	4,13w(25,6)(3)	36
* Patient 4 (employee)	8/3	S	S	S	S	R	+	---	13w(25,4,6)(3)	36
Patient 5	7/17	R	R	R	S	R	+	---	3,13w,4w(6)	36
Patient 6 7/15	7/15	NV	NV	NV	NV	NV	NV	NV	NV	NV
Dairy A										
Goat 1 (Mastitic)		I	S	I	S	R	+	---	13w,45w(25,6)(3)	36
Goat 2		S	S	S	S	S	+	---	44(25,6)	NT
Goat 3		S	S	S	S	R	+	---	8,13w,4w(25,6)(3)	36
Dairy B										
Goat 1		R	R	R	S	S	+	71 Kb	(2)(6w)	4
Goat 2		R	R	R	S	R	+	53 Kb	20	14
Goat 3		R	R	S	S	S	+	52,2	20(2)	4

NV = Non Viable

NOTE: Two family cases missing (one not cultured)

*Both from same family. Patients 1,2,5, and 6 drank the milk.

Table 3

Goat Dairies

Herd Size Approximate # of kids		Closed/open*	# wth Mastitis / Total Herd	# pos (%) / # sampled Description of the sampled goats (#+)
A	100	closed	25/100	3/10 (30%)
		(import milk)		
	Approx. kids			10 milkers (2+) 2 mastitic (1+)
B	70	open	1/70	3/10 (30%)
	20 kids			1 ram 7 milkers (1+) 1 mastitic (0-) 2 kids (2+)
C	100	closed	0/70	0/10 (30%)
	10 kids			8 milkers 2 kids

* Open herds import goats from other herds.

APPENDIX C

TABLES FROM NON-RESPONDENT SECTION OF

CASE/CONTROL STUDY

Table C-1. Interviewee.

Interviewee	Controls No. %	Non-respondents No. %
Index	335(63.7%)	51(66.2%)
Mother	182(34.6%)	18(23.4%)
Father	8(1.5%)	8(10.4%)
Other	1(0.2%)	0
Total	526	77

The overall chi-square statistic with 2 degrees of freedom calculated from the first three categories above=22.3, P=0.00001

Table C-2. Household Size in 7 before Index Date.

Size	Controls No. %	Non-respondents No. %
Solo	28(5.3%)	8(11.0%)
Couple	88(16.7%)	13(17.8%)
Trio	137(26.0%)	14(19.2%)
Quad	157(29.8%)	19(26.0%)
Quint	59(11.2%)	10(13.7%)
≥ 6	57(10.8%)	9(12.3%)
Don't know	0	4
Total	526	77

T-test statistic for the comparison of mean household size=0.4, two-tailed P=0.69.

Table C-3. Age of Index at Interview.

Age	Controls No. %	Non-respondents No. %
<1	67(12.7%)	0(0%)
1-9	117(22.2%)	19(24.7%)
10-19	35(6.7%)	8(10.4%)
20-39	211(40.1%)	32(41.6%)
≥40	96(18.3%)	18(23.4%)
Total	526	77

The T-test statistic for the comparison of mean age at interview=1.2, two-tailed P=0.23.

Table C-4. Race of Index.

Race	Controls No. %	Non-respondents No. %
White	476(91.4%)	61(82.4%)
Black	12(2.3%)	5(6.8%)
Asian	15(2.9%)	4(5.4%)
Other	18(3.5%)	4(5.4%)
Unknown	5	3
Total	526	77

The overall chi-square statistic with 3 degrees of freedom=7.0, P=0.07

Table C-5. Sex.

Sex	Controls No. %	Non-respondents No. %
Male	239(45.6%)	43(55.8%)
Female	285(54.4%)	34(44.2%)
Unknown	2	
Total	526	77

The overall chi-square statistic with 1 degree of freedom=2.8, P=0.09

Table C-6. Education Completed by Index

Education	Controls No. %	Non-respondents No. %
0 year	153(29.8%)	18(23.4%)
1-6 grades	36(7.0%)	7(9.1%)
7-8 grades	2(0.4%)	2(2.6%)
9-11 grades	25(4.9%)	2(2.6%)
12 grades	53(10.3%)	16(20.8%)
Trade school	18(3.5%)	5(6.5%)
Some college	87(16.9%)	14(18.2%)
College grad	81(15.8%)	10(13.0%)
Post graduate	59(11.5%)	3(3.9%)
Unknown	12	
Total	526	77

The T-test statistic for the comparison of the mean years of education completed by the index (restricting the analysis to indexes, 30 years of age and older, to reduce age confounding)=2.4, two-tail P=0.02.

Appendix C-3

Table C-7. Education of Mother, Wife, or Female Partner.

Education	Controls No. %	Non-respondents No. %
Grades 7-11	14(4.5%)	0(0%)
Grade 12	63(20.5%)	12(27.9%)
Trade school	15(4.9%)	4(9.3%)
Some college	95(30.9%)	6(14.0%)
College grad	78(25.4%)	11(25.6%)
Post graduate	42(13.7%)	1(2.3%)
Unknown	4	4
Does not apply	215	39
Total	526	77

The T-test statistic for the comparison of mean years of education completed by the mother, wife, or female partner of the index=0.2, two-tail P=0.84.

Table C-8. Education of Father, Husband, or Male Partner.

Education	Controls No. %	Non-respondents No. %
Grades 7-8	3(0.9%)	1(2.8%)
Grades 9-11	15(4.7%)	1(2.8%)
Grade 12	46(14.3%)	6(16.7%)
Trade school	19(5.9%)	4(11.1%)
Some college	85(26.4%)	7(19.4%)
College grad	81(25.2%)	11(30.6%)
Post college	73(22.7%)	6(16.7%)
Unknown	6	4
Does not apply	198	38

The T-test statistic for the comparison of mean years of education completed by the father, husband, or male partner of the index=0.5, two-tail P=0.62.

Table C-9. Density of Census Tract in which Index Resided at Time of Study.

Density	Controls No. %	Non-respondents No. %
<1000 per square mile	70(13.3%)	7(9.6%)
1000-4999	254(48.5%)	37(50.7%)
5000-9999	170(32.3%)	22(30.1%)
10000-14999	23(4.4%)	5(6.8%)
15000-39999	8(1.5%)	2(2.8%)
Unknown		4
Total	526	77

1)Residence at time of original selection for study was used for non-respondents who had moved.
2)The T-test statistic for the comparison of density of residential census tract=1.6, two-tail P=0.11.

Table C-10. Zip Codes.

	GHC No.	Enrollees %	Non-respondents No.	%	Controls No.	%
Rural	27,192	13.00	8	10.5	77	14.6
Suburban	70,372	33.7	33	43.4	192	36.5
Urban	111,226	53.3	35	46.1	249	47.3
or excluded unknown	--		1		8	
Total	208,790		77		526	

The overall chi-square statistic with 4 degrees of freedom=8.9, P-0.06

Table C-11. Travel.

Exposure	Controls No. %	Non-respondents No. %
Undeveloped foreign nation	1(0.2%)	0(0%)
Developed foreign nation	9(1.7%)	4(5.2%)
Within U.S.	155(29.5%)	21(27.3%)
No travel	360(68.6%)	52(67.5%)
Unknown	1	0
Total	526	77

The overall chi-square statistic with 2 degrees of freedom calculated from the last three categories=3.9, P=0.14.

Table C-12. Travel Destination.

Location	Controls No. %	Non-respondents No. %	P
King County (>30 miles from home excluding regular commuting)	48(9.1%)	10(13.0%)	0.28
Snohomish County	17(3.2%)	2(2.6%)	0.79
Pierce County	28(5.3%)	2(2.6%)	0.33
Kitsap County	7(1.3%)	1(1.3%)	1.00
Whatcom County	4(0.8%)	1(1.3%)	1.00
Island County	4(0.8%)	0(0.0%)	1.00
Skagit County	5(1.0%)	1(1.3%)	1.00
San Juan County	3(0.6%)	1(1.3%)	0.84
Grant County	0(0%)	2(2.6%)	0.03
California	4(0.8%)	1(1.3%)	0.99
Nevada	0(0%)	1(1.3%)	0.26
Canada	6(1.1%)	4(5.2%)	0.06
No Travel	360(68.4%)	52(67.5%)	0.85
Unknown	1	0	

1)The above categories are not mutually exclusive.
2)Probability value from Fisher's Exact Test of the chi-square statistic with 1 degree of freedom.

Table C-13. Outdoor Activity.

Activity	Controls No. %	Non-respondents No. %	P
Yes, any	82(15.6%)	24(37.5%)	0.0009
Alpine ski	3(0.6%)	0(0%)	1.00
Cross country ski	1(0.2%)	0(0%)	1.00
Sled	1(0.2%)	0(0%)	1.00
Other snow	1(0.2%)	0(0%)	1.00
Trail, horse	3(0.6%)	1(1.6%)	0.84
Trail, bike	5(1.0%)	5(7.8%)	0.01
Hike	23(4.4%)	11(17.9%)	0.0005
Backpack	1(0.2%)	0(0%)	1.00
Car camp	10(1.9%)	4(6.3%)	0.18
Beach	40(7.6%)	7(10.9%)	0.67
Sand box	1(0.2%)	1(1.6%)	0.48
Other	20(3.8%)	11(17.2%)	0.0006
Specific Activity Unknown	2	0	

1)The above categories are not mutually exclusive.
2)The probability value from the Fisher's exact Test or chi-square statistic with 1 degree of freedom.

Table C-14. Baby Food, Raw Milk, Chicken.

Exposure	Controls			Non-respondents			p
	Total	No. Exp	%	Total	No. Exp	%	
Baby food with meat	76	11	(14.5%)	4	1	(25.0%)	0.98
Raw milk	523	8	(1.5%)	7	3	(3.9%)	0.11
Chicken	476	325	(68.3%)	75	34	(45.3%)	0.0001
Unknown		1-21			0-2		

The probability value from Fischer's Exact Test or the chi-square with 1 degree of freedom.

Table C-15. Non-Home Surface, Well, or Bottled Water

Exposure Non-home water consumed	Controls Total	No. Exposed Exp	%	Non-respondents Total	No. Exposed Exp	%	P
From well	506	36	(7.1%)	70	5	(7.1%)	0.99
From river	523	9	(1.7%)	71	2	(2.8%)	0.78
From lake	523	8	(1.5%)	73	3	(4.1%)	0.28
From bottle	526	28	(5.3%)	77	7	(9.1%)	0.19
Unknown		3-13			0-7		

The probability value from Fisher's Exact Test or the chi-square statistic with 1 degree of freedom.

Table C-16. Number of Household Contact in Each Age Group.

Age	Controls No. Contacts	%	Non-respondents No. Contacts	%
<1 year	37	(2.6%)	2	(1.1%)
1-4 years	178	(12.5%)	21	(11.4%)
5-9 years	158	(11.1%)	25	(13.6%)
10-19 years	218	(15.3%)	29	(15.8%)
20-39 years	622	(43.5%)	71	(38.6%)
≥40 years	216	(15.1%)	36	(19.6%)
Don't know	0		5	

The T-test statistic for the comparison of mean household age (including the index)=0.25, two-tail P=0.80.

Table C-17. Number of Household Contacts of Each Sex.

Sex	Controls No. Contacts %	Non-respondents No. Contacts %
Male	736(51.4%)	91(54.8%)
Female	697(48.6%)	75(45.2%)
Unknown	0	19

The overall chi-square statistic with 1 degree of freedom=0.7, P=0.40

Table C-18. Number of Household Contacts by Their Relationship to the Control/Non-Respondent.

Relationship	Controls No. Contacts %	Non-respondents No. Contacts %
Spouse	213(14.9%)	26(13.8%)
Parent	450(31.4%)	58(30.7%)
Child	302(21.1%)	38(20.1%)
Sibling	245(17.1%)	42(22.2%)
Partner	12(0.8%)	1(0.5%)
Relative	87(6.1%)	8(4.2%)
Housemate	124(8.7%)	16(8.5%)
Unknown	0	1

The overall chi-square statistic with 6 degrees of freedom=3.9, P=0.69

Table C-19. Direct Animal Contacts.

Exposure	Controls Total	No. Exposed Exp	%	Non-respondents Total	No. Exposed Exp	%	p
Animal(includes indirect contact)	525	464(88.4)		77	68(88.3%)		0.99
Dog	521	327(62.8%)		76	54(70.1%)		0.16
Cat	522	287(55.0%)		76	39(50.6%)		0.55
Bird	520	58(11.2%)		75	11(14.5%)		0.38
Reptile	521	8(1.5%)		75	2(2.6%)		0.72
Cattle	523	9(1.7%)		75	1(1.3%)		1.00
Sheep	524	5(1.0%)		75	1(1.3%)		1.00
Pig	522	4(0.8%)		75	1(1.3%)		0.98
Goat	523	11(2.1%)		75	2(2.6%)		1.00
Fish	522	18(3.4%)		75	5(7.9%)		0.18
Rodent	521	30(5.6%)		75	5(6.6%)		0.75
Other animals	523	54(10.3%)		76	8(10.5%)		0.96

1)Information was unknown for 1-6 controls and 0-1 non-respondents.
2)The probability value from Fisher's Exact Test or the chi-square statistic with 1 degree of freedom.

Animal-to-Man Transmission of Antimicrobial-Resistant *Salmonella:* Investigations of U.S. Outbreaks, 1971–1983

Abstract. *The importance and origin of antimicrobial-resistant* Salmonella *infections were examined in 52 outbreaks investigated by the Centers for Disease Control between 1971 and 1983. The case fatality rate was higher for patients infected with antimicrobial-resistant* Salmonella *(4.2 percent) than for those with antimicrobial-sensitive infections (0.2 percent). In the 38 outbreaks with identified sources, food animals were the source of 11 (69 percent) of 16 resistant and 6 (46 percent) of 13 sensitive outbreak strains.*

Antimicrobial-resistant *Salmonella* have accounted for a steadily increasing proportion of human *Salmonella* infections and now represent approximately 20 to 30 percent of salmonellae isolated from humans (*1*, *2*). The importance of antimicrobial resistance in *Salmonella* has been questioned because most *Salmonella* infections do not require antimicrobial therapy. In addition, it has been suggested that antimicrobial-resistant *Salmonella* may be less virulent than antimicrobial-sensitive strains (*2–4*). The source of these resistant bacteria is also controversial. Some have argued that the administration of antimicrobials to animals—this use accounts for about half the antimicrobials produced yearly in the United States—selects for antimicrobial-resistant bacteria, has increased their prevalence in the food chain, and has been the principal cause of the increased incidence of drug-resistant strains in humans. However, others have argued that multiple-drug-resistant bacteria derive mainly from too frequent prescribing of antimicrobials for humans, particularly in hospitals, and that the human and animal pools of antimicrobial-resistant *Salmonella* overlap infrequently and transiently (*5*, *6*).

The major obstacle to determining whether antimicrobial-resistant bacteria often arise from food-animal sources and present an important threat to human health has been the difficulty in tracing all the postulated steps from farm practice to human disease. Individual events in the complicated sequence have been documented, such as the selection for and persistence of resistant bacteria in food-producing animals resulting from the use of subtherapeutic doses of antimicrobials (*7–11*), the frequent presence of resistant *Salmonella* in products of animal origin (*12*, *13*), the transmission of resistant microorganisms to humans (*6*, *14*), and human disease resulting from multiply resistant bacteria (*1*). However, outlining all these steps in a sequence is rarely possible and does not indicate the relative frequency with which resistant bacteria arise from animal and human populations (*15*).

It may not be possible to determine exactly how often animal-to-man transmission of resistant enteric pathogens occurs (*16*, *17*). However, it is possible to determine whether animal-to-man transmission of antimicrobial-resistant *Salmonella* has been demonstrated in an important fraction of *Salmonella* outbreaks investigated in the United States. We reviewed epidemiologic and laboratory data of all Centers for Disease Control (CDC) investigations of nontyphoidal *Salmonella* outbreaks between January 1971 and December 1983.

Summary reports were available and complete for 52 of 55 *Salmonella* outbreaks investigated by CDC personnel in the 12-year period. We could classify these outbreaks into three groups: (i) 34 that had occurred in the community; (ii) 12 that had occurred wholly within a hospital or institution; and (iii) 6 that had occurred both in the community and in a hospital (Table 1).

In only 5 of the 52 outbreaks was the antimicrobial susceptibility of the epidemic strain known at the time that the CDC was requested by state health departments to participate in these investigations. At the outset of CDC investigations, sources or modes of spread of outbreak strains were suspected in 11 of the 18 outbreaks traced to animals, in 9 of the 11 outbreaks originating from a common source, in 3 of the 4 outbreaks of another source, in 3 of the 5 outbreaks spread person-to-person in hospitals, and in 5 of the 13 outbreaks in which the source could not finally be determined.

Seventeen of the 52 outbreaks involved antimicrobial-resistant organisms and affected 312 persons, 13 of whom (4.2 percent) died from salmonellosis. Eight deaths in elderly persons were from community-acquired organisms in three outbreaks traced to raw milk and beef obtained from specific dairies and a beef herd (*18*, *19*); the 5 deaths in 18 affected infants occurred in a single hospital nursery outbreak caused by multiply resistant *S. typhimurium* of unknown source. In contrast to fatalities caused by antimicrobial-resistant organisms, the 19 outbreaks caused by antimicrobial-sensi-

Table 1. Outbreaks of salmonellosis investigated by the CDC between 1971 and 1983. Numbers in parentheses represent the number of outbreaks involving *Salmonella* resistant to two or more antimicrobials.

Source of outbreaks	Number of outbreaks			Total
	Community	Nosocomial	Both	
Food animals or their products	12 (7)	2 (1)	4 (3)	18 (11)
Common source (food-handler, restaurant, kitchen)	10 (1)	1 (0)	0	11 (1)
Other source (food, drug, lab animal, hospital equipment)	2 (0)	2 (1)	0	4 (1)
Person-to-person spread	0	5 (2)	0	5 (2)
Unknown or unproven	10 (0)	2 (1)	2 (1)	14 (2)
Total	34 (8)	12 (5)	6 (4)	52 (17)

tive *Salmonella* resulted in only 4 (0.2 percent) fatalities in 1912 ill persons. In the 16 outbreaks caused by *Salmonella* of unspecified antimicrobial resistance, 4 (0.3 percent) of 1429 ill persons died.

In the 52 outbreaks, a specific source or mode of transmission was identified for 38 (73 percent). In those 38 outbreaks, multiply resistant salmonellae were involved in 8 (33 percent) of the 24 community-based outbreaks, in 4 (40 percent) of the 10 nosocomial outbreaks, and in 3 (75 percent) of the 4 outbreaks which occurred both in community and hospital (Table 1). Epidemiologic investigation implicated food-producing animals as the source of 18 (47 percent) of the 38 outbreaks in which a source was identified (Table 2); food animals were incriminated in 11 (69 percent) of 16 outbreaks involving antimicrobial-resistant *Salmonella*, in 6 (38 percent) of 16 outbreaks caused by antimicrobial-sensitive *Salmonella*, and in 1 (11 percent) of 9 outbreaks caused by *Salmonella* of unspecified antimicrobial susceptibility.

The antimicrobial-resistant organisms were acquired by consuming contaminated foods such as raw milk or undercooked beef (Table 2), or by complex pathways of foodborne and person-to-person transmission. An example of such complex transmission was found in the investigation of outbreak 9 (Table 2): multiply resistant *S. heidelberg* was transmitted by direct contact from ill calves to a pregnant woman, who subsequently transmitted the infection at birth to her infant, and then further transmission occurred to other infants in a hospital nursery (*20*). Similar events occurred in outbreaks 12 and 18 (Table 2), in which nosocomial infections with multiply resistant *Salmonella* were shown to have ultimately come from food animals (*18, 19*). In addition to the 18 outbreaks traced to animals, investigators suspected 5 of the 14 outbreaks of unproven origin to have originated from beef cattle, poultry, or eggs.

The data presented here have unavoidable limitations. These outbreaks were investigated by the CDC at the request of state health departments and therefore are not a random sample of all *Salmonella* outbreaks. Because in over 90 percent of the outbreaks the antimicrobial susceptibility of organisms was not known at the beginning of the CDC investigations, bias in investigating outbreaks of antimicrobial-resistant *Salmonella* is probably not a major confounding variable. However, sources of 30 of the 52 outbreaks were suspected at the start of CDC investigations (although not proven in five instances); thus, a bias to investigate *Salmonella* of animal origin may confound these data. Yet, even if this is so, of the 22 outbreaks of unsuspected and unknown origin at time of investigation, 7 (57 percent) of the 13 identified sources were traced back to animals. Further, 5 of the 14 outbreaks of unproven origin were strongly suspected to have arisen from animal populations. Finally, the frequency of animal-associated outbreaks in this study is similar to that found in a study in which sources of 651 *Salmonella* outbreaks in the United States that were reported to the CDC between 1963 and 1975 were examined (*24*).

Table 2. Outbreaks investigated by the CDC with documented transmission of *Salmonella* from food animals to man, 1971 through 1983.

Outbreak	Year	Location	Serotype	Resistence*	Animal source	Comment and technique‡	Reference
1	1971	Maine	*thompson*	S	Poultry†	Feed with antibiotics given once: As	
2	1972	Montana	*typhimurium*	R	Cattle†	Five farm families: As, Ph, Tn	
3	1972	Wisconsin, Minnesota	*typhimurium*	U	Cattle	Raw beef consumption: Ph, Tn	(*20*)
4	1972	Alaska	*agona*	S	Poultry	Peruvian fish-meal suspected	(*20*)
5	1973	Alabama	*typhimurium*	R	Calves	Same organism in feed: As	
6	1973	Maine	*typhimurium*	R	Eggs	Same organism at egg farm: As, Ph	
7	1974	Washington	*typhimurium*	R	Dairy†	? Contaminated feed: As	
8	1975	Maryland	*newport*	R	Cattle†	Beef from Colorado: As, Ph	(*14*)
9	1976	Connecticut	*heidelberg*	R	Calves†	Secondary nosocomial spread: As, Pl	(*21*)
10	1976	Missouri	*thompson*	S	Cattle	Nosocomial outbreak traced to raw beef: As	
11	1977	Kentucky	*typhimurium*	R	Dairy†	Raw milk consumption: As, Ph	(*20*)
12	1979	United States	*dublin*	P	Dairies†	Raw milk consumption: As	(*18*)
13	1980	Montana	*typhimurium*	R	Dairy†	Raw milk consumption: As, Ph	(*20*)
14	1981	Pennsylvania, New Jersey	*typhimurium*	S	Cattle	Precooked roast beef: As, Ph, Pl	(*22*)
			newport	S			
15	1982	District of Columbia	*typhimurium*	S	Cattle†	Beef short ribs: As	
16	1982	Wyoming	*typhimurium*	S	Eggs†	Homemade ice cream: As, Pl	
17	1983	Arizona	*typhimurium*	R	Dairy†	Raw milk consumption: As, Pl	(*19*)
18	1983	Minnesota, South Dakota	*newport*	R	Cattle	Cattle fed subtherapeutic antibiotics in feed: As, Pl	(*19*)

*R, *Salmonella* resistant to two or more antimicrobials; S, *Salmonella* susceptible to all antimicrobials tested, and U, *Salmonella* of unspecified antimicrobial susceptibility. †Animal source suspected at the outset of the CDC investigation. ‡Techniques used to characterize organisms: As, antimicrobial susceptibility; Ph, phage lysis pattern; Tn, tartrate negativity; and Pl, plasmid profile analysis (*22*).

These investigations found that in over two-thirds of U.S. outbreaks of multiple-drug-resistant *Salmonella* infections that had a defined source, such bacteria came from food animal populations. It is known that *Salmonella* are commonly transmitted in food animal products, and our analysis shows that multiply resistant *Salmonella* are also frequently transmitted from animals to man. In fact, animal origins were discovered more commonly in outbreaks involving antimicrobial-resistant *Salmonella* than in outbreaks involving antimicrobial-sensitive strains. Thus, it appears to us that animal-to-man transmission of resistant *Salmonella* is not a rare event.

The case fatality rate for patients with identified infections with multiply resistant *Salmonella* was 4.2 percent, 21 times higher than the case fatality rate associated with antimicrobial-sensitive *Salmonella* infections. The explanation for this difference in fatality rates is not known. The fatalities in these investigations were among the old and the very young. Patients at the extremes of age may be more likely to die of salmonellosis, and these patients may have underlying conditions that would lead to antimicrobial or other drug therapy which could complicate or predispose to infection with resistant bacteria. In any case, antimicrobial-resistant *Salmonella* did not appear to be less virulent than antimicrobial-sensitive strains, and the public health significance of multiply resistant *Salmonella* should not be minimized.

We conclude that antimicrobial-resistant enteric bacteria frequently arise from food animals and can cause serious infections in humans.

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DRUG-RESISTANT SALMONELLA FROM ANIMALS FED ANTIMICROBIALS

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Abstract It has been difficult to document the postulated sequence of events that begins with the selection of drug-resistant organisms in animals fed subtherapeutic amounts of antimicrobials and ends with clinically important infections in human beings. In early 1983 we identified 18 persons in four Midwestern states who were infected with *Salmonella newport* that was resistant to ampicillin, carbenicillin, and tetracycline and characterized by a 38-kilobase R plasmid. Twelve of these patients had been taking penicillin derivatives for medical problems other than diarrhea in the 24 to 48 hours before the onset of salmonellosis. Eleven patients were hospitalized for salmonellosis for an average of eight days, and one had a fatal nosocomial infection. We compared plasmid profiles of all human (six-state area) and animal (United States) *S. newport* isolates over an 18-month period and examined selected records of meat distribution. The results indicated that the patients had been infected before they took antimicrobials, by eating hamburger originating from South Dakota beef cattle fed subtherapeutic chlortetracycline for growth promotion.

This study demonstrates that antimicrobial-resistant organisms of animal origin cause serious human illness, and emphasizes the need for more prudent use of antimicrobials in both human beings and animals. (N Engl J Med 1984; 311:617-22.)

VARIOUS gastrointestinal illnesses — from mild, self-limited diarrhea to pseudomembranous colitis — are recognized complications of treatment with antimicrobials.[1] Less appreciated, however, is the clinical expression of previously asymptomatic infections with antimicrobial-resistant enteric bacteria after the use of antimicrobials. Only a single case of severe illness due to antimicrobial-resistant salmonella beginning after antimicrobial therapy has been previously reported.[2]

Multiple drug-resistant isolates have accounted for a steadily increasing percentage of human salmonella infections[3] and now represent approximately 20 to 25 per cent of identified cases.[4,5] The source of these resistant enteric pathogens in persons is controversial,[6-8] but many believe that subtherapeutic amounts of antimicrobials administered to animals in their feed for "growth promotion" or "disease prevention" select for resistant bacteria that eventually infect people. About half the antimicrobials produced in the United States yearly are fed to farm animals, but proof of the emergence of drug-resistant enteric pathogens in food animals fed subtherapeutic amounts has been difficult to obtain because of the complex sequence of events between farming practices and human disease.[9]

In early February 1983, laboratory-based surveillance of salmonella infections by the Minnesota Department of Health showed that there was a marked increase in isolates of *Salmonella newport (S. enteritidis* serotype *newport)* and that many of the patients contacted had been taking antibiotics for nondiarrheal illnesses just before the onset of salmonellosis. An investigation was begun to examine the possibility that the outbreak was caused by a contaminated antimicrobial. This hypothesis was rejected since the patients had taken different antimicrobials from different pharmacies and manufacturers. We describe here the results of subsequent investigations in a six-state area, which indicated that taking antimicrobials may provide a selective advantage for resistant enteric bacteria causing serious illness, and that food animals were the source of the multiply resistant *S. newport*.

METHODS

All patients in a recognized cluster of 10 cases of *S. newport* infection in Minnesota (early 1983) were interviewed for histories of foods eaten, antimicrobial use, clinical illness, hospitalization, travel, and illness in family members. For comparison with the outbreak cases, we interviewed and obtained isolates from 11 of 12 patients with *S. newport* infections that were reported to the Minnesota Department of Health in 1982 and from 27 of 30 patients with salmonellosis (serotypes other than *S. newport*) reported in Minnesota in the first two months of 1983.

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After the investigation in Minnesota, we reviewed state and federal surveillance records for Minnesota, South Dakota, North Dakota, Iowa, Wisconsin, and Nebraska and obtained all available human isolates of *S. newport* in the six-state area for 1982 and the first half of 1983. After determining which isolates had the same pattern of antimicrobial resistance and the same plasmid profile as the isolates from the outbreak in Minnesota, we interviewed the patients for the same information as obtained from the patients in the Minnesota outbreak.

All salmonella isolates, including those from comparison groups, were tested for antimicrobial resistance by means of standard Kirby–Bauer disks.[10] The plasmid DNA from *S. newport* isolates resistant to ampicillin, carbenicillin, and tetracycline was analyzed according to a modification of a technique described by Birnboim and Doly.[11] Plasmids were further characterized by restriction-endonuclease digestion with *Hind*III according to the manufacturer's instructions (Bethesda Research Laboratories).

To determine whether antibiotic resistance was plasmid-mediated (R plasmid), we attempted to transfer resistance from the epidemic *S. newport* by broth and filter matings with nalidixic acid–resistant strains of *Escherichia coli* (185 and C600) and rifampin-resistant *S. heidelberg*. In addition, *E. coli* C600 was transformed with plasmid DNA extracted from *S. newport* isolates from the outbreak and comparison groups.[12] We attempted to cure *S. newport* of antibiotic resistance by growth at 42°C and by exposure to varying concentrations of acridine orange, sodium dodecyl sulfate, and ethidium bromide.[11] Plasmid DNA was hybridized with a ^{32}P-labeled beta-lactamase gene probe (prepared by Robert C. Cooksey, Ph.D., Centers for Disease Control). The probe was obtained by electroelution of a 1-kb (kilobase) fragment after sequential restriction-endonuclease digestion of pBR322 plasmid DNA with *Eco*RI and *Hin*fI.

We obtained all available *S. newport* strains isolated from livestock and poultry in the six-state area in 1982 and the first half of 1983, as well as all nonhuman strains isolated in the United States from October 1981 through September 1982 (U.S. Department of Agriculture, National Veterinary Service Laboratory, Ames, Iowa). If livestock isolates showed the same antimicrobial-resistance pattern and plasmid profile as those from the outbreak group, we contacted owners about feeding, purchasing, sales, and antimicrobials added to feed for their herds. The distribution of all products from these herds was traced, when applicable, through sales, processing, and distribution centers.

Table 1. Findings in 18 Cases of Multiply Resistant *S. newport* Infection.

Patient No.	Age/Sex	Date of Onset	Antimicrobial (Days Started)	Days in Hospital	Hamburger from Herd *	Comments
South Dakota outbreak						
1	29/F	12/13/82	Amoxicillin (12/11)	17	Yes	
2	3/F	12/13/82	Amoxicillin (12/11)	4	Yes	Daughter of Pt. 1
3	69/M	12/27/82	Multiple (12/15–1/10)	13 †	No	Secondary case ‡
4	33/M	2/14/83	Penicillin (2/11)	8	Yes	Dairy-herd owner
Minnesota outbreak						
5	20/M	1/18/83	Penicillin (1/10)	5	Yes	
6	33/F	1/26/83	Amoxicillin (1/25)	8	Yes	
7	43/F	1/28/83	None	0	Yes	
8	43/F	1/29/83	None	0	No	
9	20/F	1/31/83	None	6	Yes	"Cold" (1/24)
10	34/F	2/1/83	Penicillin (1/26)	0	No	
11	8/F	2/1/83	Amoxicillin (1/30)	4	No	
12	33/M	2/2/83	Amoxicillin (1/31)	5	Yes	Husband of Pt.6
13	20/F	2/6/83	Amoxicillin (2/4)	13	Yes	
14	37/F	2/8/83	Penicillin (2/7)	0	Yes	
Other cases						
15	18/F	2/5/83	None	0	No	North Dakota
16	30/M	2/10/83	Penicillin (2/8)	6	Yes	Iowa
17	6/M	4/14/83	None	0	Yes	Son of Pt. 4
18	17/M	5/4/83	None	0	Yes	Son of Pt. 7

*Hamburger at home suppliad directly from the suspected herd or purchased from markets thought to be supplied with meat from the herd.

†Days between onset of diarrhea and death in hospital

‡Patient underwent endoscopy directly after Patient 1

Results

In the initial investigation in Minnesota, we identified 10 patients with multiply resistant *S. newport* infection with dates of onset between January 18 and February 8, 1983. These patients ranged in age from 8 to 43 years (mean, 30; median, 33) (Table 1); eight lived in the Minneapolis–St. Paul metropolitan area (Fig. 1). Of the 10 cases, 7 had taken amoxicillin or penicillin in the week before the onset of illness (Table 1); 2 had taken leftover antibiotics without physician supervision. Five of the seven using antimicrobials had started taking penicillin derivatives within the 48 hours before the onset of symptoms of salmonellosis. Four users of amoxicillin had been taking it for bronchitis (two patients), thyroiditis (one patient), or otitis media (one patient); three users of oral penicillin took it for pharyngitis. The duration of illness before patients took antimicrobials was 1 and 3 days for the two patients with bronchitis and 2, 4, and 21 days for the three patients with pharyngitis, respectively. One person who had not taken antimicrobials before illness had had symptoms of a "cold" in the week before the onset of salmonellosis. In contrast, none of 11 patients with sensitive *S. newport* infections in 1982 had taken penicillin derivatives in the four weeks before their illnesses ($P = 0.001$, odds ratio = 51.3 [Fisher's two-tailed exact test]), and only 2 of 27 patients with recent non-*S. newport* salmonellosis had taken antimicrobials (cephaloridine or amoxicillin) in the four weeks before their illnesses ($P = 0.0004$, odds ratio = 29.2). None of 30 household contacts of the 10 patients in the Minnesota outbreak took antimicrobials or became ill, except for the contact who was also a patient (Patient 12).

Six of the Minnesota outbreak group were hospitalized for salmonellosis for an average of eight days (Table 1). All 10 in the group had diarrhea (defined as three or more loose stools in 24 hours), abdominal cramps, and nausea. Nine patients had documented fever (temperature above 38°C) with concurrent chills, eight had one or more episodes of vomiting, and six had blood in their stools.

In the subsequent investigation in the six-state area, we found four more cases of infection in South Dakota (Patients 1 through 4) with *S. newport* of the same antimicrobial-resistance pattern as in the Minnesota cases; all four patients had taken penicillins — one without physician supervision — before the onset of salmonellosis (Table 1). Patients 1 and 2 had had bronchitis for seven days before they took amoxicillin, and Patient 4 had had pharyngitis for four days before

he took penicillin. Patient 3 (Table 1) had been admitted to the same hospital as Patient 1 for abdominal trauma, which was treated by splenectomy; diarrhea developed eight days after sigmoidoscopy, which had been performed in preparation for hemicolectomy. Hospital records showed that Patient 3 underwent sigmoidoscopy immediately after Patient 1, and that his endoscopy was performed by the same staff and with the same equipment. The sigmoidoscope had been put for 10 minutes in a glutaraldehyde-phenate solution (0.13 per cent glutaraldehyde) that had been in use for about 25 days. During his hospital stay, Patient 3 received many antimicrobials and died with fever, confusion, and other symptoms of septicemia 20 days after the endoscopy. *S. newport* resistant to ampicillin, carbenicillin, and tetracycline was isolated from blood, sputum, and stool before he died.

The isolates from the 10 cases in Minnesota and the isolate available from one case in South Dakota (Patient 4) were all resistant to ampicillin, carbenicillin, and tetracycline and had the same plasmid profile and endonuclease restriction pattern of plasmid DNA (Fig. 2). These characteristics were identical to those of an *S. newport* strain isolated from the tissues of a calf that died during an outbreak of diarrheal disease in Patient 4's dairy cows in November 1982 (Fig. 2).

From laboratory analysis of 72 human isolates submitted to health-department laboratories in the six-state area from January 1982 through June 1983, we found four more *S. newport* isolates with the epidemic antimicrobial-resistance pattern and distinctive 38-kb plasmid seen in outbreak isolates. The four cases of the epidemic *S. newport* strain occurred during or after the 14 cases of the outbreaks in Minnesota and South Dakota. Two of the four patients (Patients 17 and 18) lived with outbreak patients (Patients 4 and 7); we were unable to determine whether their infections were acquired from food also eaten by outbreak patients (frozen hamburger or raw milk) or from secondary spread from outbreak patients. Patient 16 (Iowa) was ill during the outbreak in Minnesota. Like many of the outbreak patients, he had taken an antimicrobial before becoming ill (penicillin for a sore throat during the two days before the onset of diarrhea) and was hospitalized for salmonellosis (Table 1). Before her illness Patient 15 (North Dakota) ate most of her meals at a college cafeteria and was unable to specify the foods eaten. An additional isolate obtained from a patient in Wisconsin in 1982 contained the 38-kb plasmid, but in association with a 5.1-kb plasmid that was not present in the outbreak isolates; moreover, this patient acquired the infection in Mexico or Texas.

Figure 1. Distribution of 18 Cases of Resistant *Salmonella newport* Infection (Circled Numerals) in Relation to Origin and Shipment of Infected Beef, December 1982 through June 1983.

Broken lines denote suspected routes of shipment.

Epidemiologic investigation in Minnesota to determine the source of the epidemic *S. newport* revealed that the patients had eaten no unusual foods, but all had eaten ground beef (hamburger) in the week before illness. Seven of the 10 patients in Minnesota were women who prepared food, among whom two said they might have tasted raw hamburger before cooking it. Three South Dakota patients (No. 1, 2, and 4) lived on two farms and were related by marriage, but they had not eaten together or socialized with one another in the previous year. The only common place of exposure for these patients was a relative's feedlot beef farm, which was adjacent to the farm of Patient 4's dairy herd. Patients 1, 2, and 4 had received beef directly from the beef herd in 1982 and 1983.

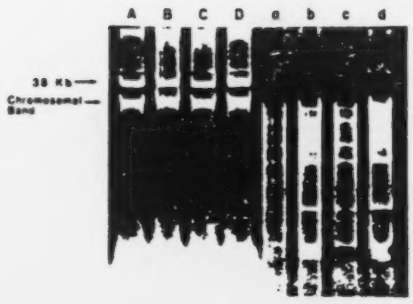

Figure 2. Agarose Gel Electrophoresis of Plasmids (Lanes A through D) and *HindIII* Endonuclease Restriction Fragments (Lanes a through d) Showing Identity of Human and Livestock *S. newport* Isolates from Minnesota and South Dakota.

Lanes A and a are from the South Dakota dairy herd, November 1982; B and b, from the owner of this herd, March 1983; and C and c and D and d, from two patients in the Minnesota outbreak, January through February 1983.

The beef cattle had been fed subtherapeutic amounts of chlortetracycline throughout 1982 for growth promotion and disease prevention, but no therapeutic concentrations of antimicrobials. The farmer added chlortetracycline to the feed by hand, approximately 100 g per ton (0.9 metric ton) of feed. All 105 head from this herd had been slaughtered in Minnesota in January 1983, and 59 carcasses were sent to Nebraska for processing into boxed beef (Fig. 1). (Boxed beef is usually sold to supermarket chains, which grind it into hamburger.) Of the other 46 carcasses, 12 could be traced to a vocational school in Minnesota that trained butchers; *S. newport* was not recovered from anyone in the area to which the vocational school supplied beef. On the day after the 59 carcasses had been cut and packed in boxes in Nebraska, 40,000 lb (18,000 kg) of boxed beef — which could have included meat from both the suspect herd and other herds — were sent to a meat-brokerage firm near Minneapolis–St. Paul. The boxes were traced through the computerized records of the meat broker to six to seven supermarkets named as the source of ground beef by the eight patients in the initial outbreak who lived in the Minneapolis–St. Paul area. Also, three days after the beef had been processed in Nebraska, 30,000 lb (14,000 kg) of "50:50 trim," which is also used for hamburger, were shipped to a meat-brokerage firm that supplied supermarkets used by Patients 5 (southern Minnesota) and 16 (Iowa) (Fig. 1).

We obtained and analyzed 91 nonhuman *S. newport* isolates from the National Veterinary Services Laboratories — 9 isolates from the six-state area in 1982 and the first half of 1983, and 82 isolates from throughout the continental United States from October 1981 through September 1982. Only the isolate from the dairy herd of Patient 4 had exactly the same antimicrobial-resistance pattern and plasmid profile as the isolates from patients in the outbreak groups (Fig. 2). Another 10 nonhuman isolates from Texas (two from swine and two from rabbits), Pennsylvania (three from cattle), Nebraska (one from cattle and one from swine), and Kentucky (one from a horse) had the same antimicrobial resistance and 38-kb plasmid as the isolates from the outbreak groups but also had a 5.1-kb plasmid and were resistant to sulfadiazine. These animal infections occurred before infection of the South Dakota dairy herd (November 1982) and the first cases of human infection (December 1982).

The 38-kb plasmid was not transferable by conjugation or transformation and could not be mobilized. The resistances shown by epidemic *S. newport* were not overcome by growth at high temperature or exposure to curing agents. However, plasmid DNA from the epidemic *S. newport* hybridized with the labeled DNA probe containing a gene sequence coding for beta-lactamase.

Discussion

Our data indicate that multiply resistant *S. newport* caused serious disease in 18 persons in four states, 12 of whom had taken antimicrobials to which the organism was resistant. The patients took these drugs — in three instances without the direction of a physician — for nondiarrheal medical disorders such as pharyngitis and usually became ill within 24 to 48 hours after starting their medication. In addition to the rarity of pharyngitis and bronchitis as symptoms of nontyphoidal salmonellosis, their long duration in eight patients (average of eight days for pharyngitis and four days for bronchitis) before these patients took antimicrobials makes it unlikely that these symptoms were part of the prodrome of salmonellosis. Rather, the rapid onset of gastrointestinal illness after antimicrobial use suggested that most of these patients had an asymptomatic infection, and that the use of antimicrobials to which the *S. newport* was resistant constituted selective pressure that allowed growth of the organism. The histories of two patients — one taking penicillin for a week, and another having a cold for a week before the onset of salmonellosis — suggested that the converse also occurred — i.e., changes in gut flora preceded infection with resistant bacteria. Recent work by Riley et al. has shown that use of penicillin derivatives in the four weeks before salmonellosis is a significant risk factor for disease from resistant organisms.[13] This risk may result because antimicrobials allow the clinical expression of previously asymptomatic infections with resistant bacteria.

The number of cases of asymptomatic and mild infection with multiply resistant *S. newport* in these outbreaks is unknown, but it could be large since approximately 40,000 lb of potentially contaminated meat were distributed in the Minneapolis–St. Paul area. A previous study of *S. newport* transmitted in raw hamburger showed that an increased occurrence of sal-

monellosis in women 20 to 40 years old was associated with their tendency to taste hamburger before or while cooking it.[14] Although only two of the patients in our study admitted to this tendency, half the identified cases occurred in female food preparers, and food preparation alone may increase the risk of infection.[15] Although the meat distributed to the area may not have been uniformly contaminated, families of patients were likely to have eaten the same ground beef as the patients and may have been infected too. Among the 30 household contacts of Minnesota patients, only Patient 12 took antimicrobials; salmonellosis developed 48 hours after he had taken two capsules of amoxicillin used by his wife (Patient 6) six days before. Many people taking antimicrobials for common illnesses such as pharyngitis[16,17] may be at risk of serious illness if they are already inapparently infected with antibiotic-resistant enteric pathogens.

Epidemiologic and laboratory investigations suggested that the source of the resistant salmonella was a beef herd in South Dakota. Although suspect hamburger was not available for culture, the exposures of the ill persons in Minnesota, South Dakota, and Iowa coincided with the distribution of the meat. In addition, the only human (six-state area) or animal (United States) isolate of the epidemic strain of *S. newport* in the year before the outbreaks was from dairy cows on a farm adjacent to the farm of the beef herd.

The ultimate source of the R plasmid found in the epidemic salmonella strain is unknown. Analysis of *S. newport* from animals and human beings in the United States in the year before the outbreaks revealed the 38-kb plasmid, in association with other plasmids, in isolates from 10 animal populations in four states in 1981 and 1982 and one patient with infection acquired in Mexico or Texas in June 1982. Thus, the beef herd was probably not the original source of the R plasmid, but the use of subtherapeutic tetracycline in the herd's feed throughout 1982 provided a selective pressure for persistence of the antimicrobial-resistant organism.[18-20] Addition of antimicrobials to feeds at subtherapeutic concentrations to enhance growth of food animals is a common practice, and this use encourages not only the persistence of resistant bacteria but also the acquisition of resistance.[18-23]

Transfer of antimicrobial-resistant bacteria from animals to human beings under natural conditions is thought to be frequent but impossible to determine accurately.[8,9,24-26] Determination of all steps from farm to consumer is difficult because of the complex sequence of events from selection for resistant bacteria[18-23] to transmission in food[14,27] and ascertainment of resultant disease. The difficulty in documenting these events in sequence has been important in the controversy over antimicrobials in animal feed, since the lack of the kind of evidence shown in these studies has been cited by proponents of antimicrobial feed additives as demonstration of their safety.

Such complicated steps in transmission obscure the actual source of antimicrobial-resistant bacteria, as in institutional outbreaks that may actually derive from animal reservoirs.[28,29] In the outbreak that we have described, *S. newport* of animal origin apparently contaminated a sigmoidoscope, which may have been inadequately disinfected,[30] and eventually resulted in a fatal case of nosocomial salmonellosis. In addition, two household contacts of outbreak patients became ill long after the outbreak had ended, suggesting secondary spread from family members. These cases of apparent person-to-person spread were ultimately of animal origin, suggesting that controversy regarding the relative importance of person-to-person transfer of enteric bacteria as compared with animal-to-person transfer[7,31,32] may be based on an artificial distinction. Recent studies[33] corroborate our suggestion that sporadic cases of salmonella infection continue to occur after introduction of bacteria through contaminated meat products.

We conclude that antimicrobial-resistant bacteria of animal origin can cause serious human disease, especially in persons taking antimicrobials, and that the emergence and selection of such organisms are complications of subtherapeutic antimicrobial use in animals. We advocate more prudent use of antimicrobials in both people and animals.

We are indebted to the following persons for assistance in investigating the Minnesota cases: Karen E. White, M.P.H., Jack A. Korlath, M.P.H., and Joel N. Kuritsky, M.D. (Acute Disease Epidemiology Section, Minnesota Department of Health), Darwin E. Zaake, Pharm.D. (St. Paul–Ramsey Medical Center), John M. Lanier (Minneapolis Center for Microbiological Investigations), John Feldman, Jeffrey Spykerman, David Yost, and Gary Quam (Minneapolis Office, U.S. Food and Drug Administration), and John G. McCullough, B.A., and Juanita E. Heiser, B.A. (Minneapolis Department of Health).

We are also indebted to Bob Cooksey, Ph.D., and Nancy Clark, M.S. (Antimicrobics and Infectious Mechanisms Branch, Centers for Disease Control), for performing DNA hybridization between the R plasmid and their labeled probe; to Janice Haney, B.S., and Joy Wells, M.S. (Enteric Bacteriology Laboratory, Centers for Disease Control), and Mr. David Janssen (Wisconsin State Hygienic Laboratory) for testing isolates for antimicrobial susceptibility; to Kris Birkness, B.A., for performing preliminary plasmid analysis of isolates from some outbreak cases; and to Billie Blackburn, D.V.M. (U.S. Department of Agriculture, Iowa) for supplying all nonhuman *S. newport* isolates.

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November 20, 1984

Hon. Margaret M. Heckler
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Services
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Dear Secretary Heckler:

The Natural Resources Defense Council, Inc. (NRDC) requests that you act immediately to suspend approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds. On the basis of recent scientific evidence, it is estimated that hundreds of thousands of people are placed at risk and hundreds of human deaths may result each year from such use of these antibiotics.

In 1977, the FDA initiated proceedings to withdraw approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds. The withdrawal procedures, however, were delayed by, among other things, Congressional advice to the FDA to postpone action until more conclusive studies were completed.

Now, recent studies have incontrovertibly shown that a serious public health threat exists. These studies show that (1) widespread use of subtherapeutic doses of penicillin and tetracyclines in animal feeds contributes to the development of bacteria resistant to these drugs; (2) antibiotic-resistant bacteria in animals can be transmitted to humans; and (3) the transmission of strains of bacteria resistant to these antibiotic drugs poses a serious threat to the public health.

In light of these studies, the FDA should renew its efforts to ban such uses of these drugs. In the meantime, you, as Secretary of Health and Human Services, should act immediately to suspend approval of such uses of these drugs because of the imminent hazard to public health.

The subtherapeutic use of antibiotics in animal feeds has been a major concern of the Natural Resources Defense Council for over a decade. In 1972, in response to a FDA proposed statement of policy,[1] NRDC sent comments to the FDA urging the withdrawal of approvals of subtherapeutic use of antibiotics and sulfonamides in animal feeds. Before Congress, NRDC submitted an extensive statement encouraging passage of H.R. 7285, a bill which would have required FDA to regulate subtherapeutic uses of antibiotics in animal feeds.[2]

When industry petitioned FDA in 1981 to vacate proposed actions that would limit the use of antibiotics in animal feed, NRDC countered with petitions to the contrary.[3] In 1983, NRDC filed extensive comments vigorously opposing FDA's proposed rule that would have allowed new approvals of subtherapeutic use of penicillin and tetracycline in animal feeds for the first time in ten years.[4]

Most recently, on October 22, 1983, NRDC sent President Reagan and you a letter requesting a ban on the subtherapeutic use of penicillin and tetracyclines in livestock feeds. Over 300 scientists supported the requested ban, including some of this country's leading scientists, physicians, and biologists. Since 1979, NRDC's activities in this area have been overseen by its Antibiotic Science Advisory Committee, members of which are all experts in this field. (See attached list.)

NRDC's petition requesting immediate suspension is enclosed. It provides detailed documentation of why suspension should be ordered.

We hope you will give this issue the very serious consideration it deserves and that you will act immediately to suspend approval of subtherapeutic use of penicillin and tetracyclines in animal feeds.

Respectfully submitted,

Karim Ahmed

A. Karim Ahmed, Ph.D.
Senior Staff Scientist

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1 37 Fed. Reg. 2444 (Feb. 1, 1972).

2 See Antibiotics in Animal Feed: Hearing Before the Subcommitee on Health and Environment of the House Comm. on Interstate and Foreign Commerce, 96th Cong., 2nd Sess. 533 (1980).

3 See 48 Fed. Reg. 4554 (Feb. 1, 1983) (denying petitions).

4 48 Fed. Reg. 4490 (Feb. 1, 1983)(proposed rule).

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PETITION

of the

NATURAL RESOURCES DEFENSE COUNCIL, INC.

to the

SECRETARY OF HEALTH AND HUMAN SERVICES

REQUESTING
IMMEDIATE SUSPENSION OF APPROVAL OF THE
SUBTHERAPEUTIC USE OF
PENICILLIN AND TETRACYCLINES
IN ANIMAL FEEDS

November 20, 1984

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The Natural Resources Defense Council, Inc. (NRDC) hereby petitions the Secretary of Health and Human Services to suspend immediately approval of the subtherapeutic use of penicillin and tetracyclines in animal feeds, pursuant to Section 512(e)(1) of the Food, Drug and Cosmetic Act, 21 U.S.C. § 360b(e)(1). This section of law authorizes the Secretary of Health and Human Services to suspend approval of an application for use of a new animal drug if "there is an imminent hazard" to the health of man or of the animals for which the drug is intended.

NRDC submits that an imminent hazard to the public health is posed by the subtherapeutic use of penicillin and tetracyclines in animal feeds. Recent studies have confirmed that (1) widespread use of subtherapeutic dosages of these drugs in animal feeds contributes to the development of bacterial resistance to these drugs and (2) the presence in the environment of strains of resistant bacteria to these antibiotic drugs poses a serious threat to the public health.

In 1977, the FDA initiated withdrawal proceedings with respect to its approval of the use of subtherapeutic doses of penicillin and tetracyclines in animal feeds. The withdrawal procedure was, however, held up by, among other things, Congressional advice to the FDA to postpone action until more conclusive studies were completed.

Recently, newly published studies have conclusively confirmed that a serious public health threat exists. In light of these studies, FDA should renew its efforts to ban subtherapeutic

use of these drugs in animal feeds. In the meantime, suspension of approval, pending completion of administrative proceedings for withdrawal, should be ordered.

I. CRITERIA FOR SUSPENSION

The criteria the Secretary has proposed be used in determining whether an "imminent hazard" exists and, consequently, whether approval of a drug application should be suspended pending withdrawal proceedings are:

(A) The likelihood that, after the customary administrative process is completed, the product will be withdrawn from the market;

(B) The severity of the harm that could be caused by the product during the completion of customary administrative proceedings to withdraw the product from the market;

(C) The likelihood that the product will cause such harm while the administrative process is being completed;

(D) The risk to the health of humans or animals currently taking the product that might be occasioned by the immediate removal of the product from the market, taking into account the availability of alternatives to the product and the steps necessary for affected persons to adjust to these other alternatives; and

(E) The availability of other approaches to protect the public health.

44 Fed. Reg. 48,979 (to be codified at 21 C.F.R. §2.1) (proposed August 21, 1979) (proposed rule establishing imminent hazard criteria and procedure).

Similar criteria were employed by then-Secretary Joseph Califano in suspending approval of new human drug applications for phenormin hydrochloride. Order of the Secretary Suspending Approval, New Drug Application for Phenformin (July 25, 1977).

These criteria were upheld in the face of legal challenge. The district court for the District of Columbia, refusing to enjoin enforcement of the Phenformin suspension order, held that the Secretary's criteria properly reflected Congressional intent as to imminent hazard. Forsham v. Califano, 442 F. Supp. 203 (D.D.C. 1977), dismissed as moot per curiam, No. 77-1478 (D.C. Cir. 1979). The district court expressed approval of the Secretary's interpretation of imminent hazard, stating:

> [W]e are not inclined to adopt plaintiff's "crisis" interpretation of imminent hazard. Rather we are more persuaded by defendant's suggested analogy to cases interpreting the imminent hazard provisions of the Federal Insecticide, Fungicide and Rodenticide Act which caution "against any approach to the term imminent hazard...that restricts it to a concept of crisis" and adopt the view that "It is enough that there is substantial likelihood that serious harm will be experienced during any realistic projection of the administrative process." See Environmental Defense Fund v. EPA, 510 F.2d 1292, 1297 (1975); Environmental Defense Fund v. EPA, 465 F.2d 528, 540 (1972).

Id. at 208.

To justify invocation of the imminent hazard provision, what must be shown is that there is a substantial likelihood that serious harm would occur pending completion of normal administrative proceedings. The harm need not be immediate. Rather, consideration of the seriousness of the harm extends to "long-term effects that may be initiated during that period, the final anticipated injury from which occurs later." 44 Fed. Reg. at 48,981. The development of antibiotic-resistant strains of bacteria is just such a long-term effect. It is closely analogous to the long-term environmental contamination and carcinogenic risks caused by certain pesticides summarily suspended under the imminent hazard provision of the Federal

Insecticide, Fungicide and Rodenticide Act ("FIFRA"), 7 U.S.C. §136d(c). Several cases approving the application of the imminent hazard provision of that act, e.g., Environmental Defense Fund v. EPA, 510 F.2d 1292 (D.C. Cir. 1975) (aldrin/dieldrin), Environmental Defense Fund v. EPA, 548 F.2d 998 (D.C. Cir. 1976), cert. denied, 431 U.S. 925 (1977) (heptachlor/chlordane), are discussed as precedent in Secretary Califano's Order on phenformin and the proposed rule (44 Fed. Reg. at 48,981).

NRDC submits that the criteria for invoking the "imminent hazard" provision of the Food, Drug and Cosmetic Act, 21 U.S.C. § 360b(e)(1), have been met with respect to the subtherapeutic use of penicillin and tetracyclines in animal feeds. The reasons are set forth below.

II. APPLICATION OF CRITERIA

A. Likelihood of Withdrawal

The first criterion to be used in deciding whether an imminent hazard exists is the likelihood that FDA approval of the drug application will be withdrawn. 44 Fed. Reg. at 48,982. Section 360b(e)(1)(B) requires the FDA to withdraw approval of a new animal drug application when new evidence shows that the drug is not shown to be safe. Because new evidence clearly demonstrates that subtherapeutic use of penicillin and tetracyclines in animal feeds is not shown to be safe, there is a substantial likelihood that the FDA will withdraw its approval.

Indeed, in 1977, based on numerous studies demonstrating the health hazards associated with the subtherapeutic use of penicillin and tetracyclines in animal feeds, the FDA concluded that such use of these antibiotics had not been shown to be safe and proposed to withdraw its approval for such uses. 42 Fed. Reg. 43,772 (Aug. 30, 1977) (penicillin); 42 Fed. Reg. 56,264 (Oct. 21, 1977) (tetracyclines). Since 1977, additional scientific evidence has been gathered which demonstrates overwhelmingly the need for withdrawal.

1. FDA Proposed Withdrawal and Findings, 1977

In 1977, based on data it had collected from independent studies and from the drug industry, the FDA found that the use of penicillin and tetracyclines in animal feeds posed a serious human health threat and initiated withdrawal proceedings. The Director of the FDA's Bureau of Veterinary Medicine (now the Center for Veterinary Medicine) presented a detailed analysis of the scientific evidence with respect to penicillin in the notice of opportunity for hearing. 42 Fed. Reg. 43,772 (August 30, 1977). In the summary, the Director concluded:

> Evidence demonstrates that the use of subtherapeutic levels of penicillin and other antibiotics in animal feed contributes to the increase in antibiotic resistant E. coli and in the subsequent transfer of this resistance to Salmonella. Further, many strains of E. Coli and Salmonella infect both man and animals.
>
> The holders of approved NADA's have submitted no evidence to demonstrate that the observed strains of E. Coli and Salmonella in man and animals are mutually exclusive; in fact, the evidence is overwhelming to the contrary. Furthermore, in some cases the R-plasmids as well as the resistance genes from human and animal sources are indistinguishable. Thus, the potential for harm exists, as illustrated by the studies submitted and verified by evidence

> from studies conducted by independent scientists. No evidence has been submitted by any NADA holder to resolve conclusively the safety questions raised by this potential...

42 Fed. Reg. at 43,775.

The Director concluded that subtherapeutic use of penicillin creates a selective pressure on bacteria in animals to develop strains resistant to penicllin and related anti-bacterial drugs. 42 Fed. Reg. at 43,776. These bacteria, present in the animals' systems, are released into the human environment, either through direct contact of humans with farm animal or their feces, or more likely through the presence of the bacteria in animal and dairy food products. 42 Fed. Reg. at 43,776-7.

The Director was further concerned that subtherapeutic use of penicillin in animal feeds might compromise the treatment of animal diseases with antibiotics. 42 Fed. Reg. at 43,787-8. The Director found that studies submitted by industry did not alleviate this concern or show the drug to be safe.

The Director found that subtherapeutic uses of tetracyclines in animal feeds produce effects similar to those produced by penicillin. 42 Fed. Reg. 56,264. The findings as to tetracycline are based on much of the same evidence as, and are substantially similar to those for penicillin. On the basis of these findings, FDA proposed to withdraw approval of most subtherapeutic uses of tetracyclines in animal feeds.

Neither the proposed withdrawal for penicillin nor tetracyclines became final.

2. Recent Scientific Evidence, 1982-1984

(a) O'Brien et al. Study

In 1982, Dr. Thomas O'Brien and his associates at Harvard Medical School reported a study of antibiotic-resistant Salmonella bacteria (Salmonella typhimurium var. copenhagen) taken from people and food animals in several states in the United States.[1] This study isolated from the bacteria the pieces of non-chromosomal genetic material called plasmids which carry antibiotic resistance. Using a new biochemical technique to analyze the plasmids' DNA structure, the O'Brien study could identify related bacterial strains by comparing DNA fragments from plasmids in different bacteria in a variety of host organisms.

The O'Brien study found that plasmids from bacteria obtained from humans were genetically related to plasmids in bacteria isolated from animals. In fact, certain plasmids found in bacteria in human and animals were virtually identical. The similarity between the strain of bacteria and its plasmids from humans and animals in this study provides very strong evidence that antibiotic-resistant bacteria are transmitted between animals and humans on a widespread basis.

The above study also found similar or identical plasmid in bacteria from humans in widely-dispersed geographic locations. They were all identical to a plasmid carried by a single widely dispersed Salmonella strain in animals. The appearance of

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1 O'Brien, et al., Molecular Epidemiology of Antibiotic Resistance in Salmonella from Animals and Human Beings in the United States, 307 New Eng. J. Med. 1 (1982).

similar plasmids in human bacteria in a variety of places among persons having no direct contact with food animals is strong support for the contention that these antibiotic-resistant bacteria are being transmitted from animals to humans through the food chain. The above finding can only be explained by multiple independent incidents of transfer of antibiotic-resistant strain Salmonella from animals to humans.

(b) Holmberg et al. Study

In 1983, Dr. Scott Holmberg and his associates from the Centers for Disease Control in Atlanta conducted a study of 18 patients from four midwestern states who had contracted infections of Salmonella newport with identical plasmid profiles and multiple antibiotic resistance.[2] Holmberg and his associates concluded that the source of the Salmonella bacteria of all 18 patients was a single beef herd in South Dakota. The only human (six-state area) or animal (United States) isolate of this strain of Salmonella newport in the year before the outbreaks was from dairy cows on a South Dakota farm adjacent to a feedlot beef farm. Several of the 18 persons studied were known to have consumed beef directly from the herd and epidemiological evidence based on the distribution of the meat indicated that other patients also consumed beef which originated from the single feedlot beef farm. The beef herd had been fed subtherapeutic levels of chlortetracycline for over a year before the first human subject became ill.

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2 Holmberg, et al., Drug-Resistant Salmonella from Animals Fed Antimicrobials, 311 New Eng. J. Med. 617 (1984).

The Holmberg study has extraordinary significance for illustrating the risk to human health from the use of antimicrobials in animal feed. This is the first definitive study to directly link subtherapeutic use of antibiotics in animals to human disease and death (one of the 18 subjects in Holmberg's study died from Salmonella infection). The Holmberg study demonstrates that antimicrobial-resistant bacteria in animals can be transmitted to and colonize in humans. Before now, this contention was probably the most disputed of all the steps involved in establishing the human health risks associated with the feeding of antimicrobials to animals. 42 Fed. Reg. at 43,776.

Another important finding of the Holmberg study is the observation that many patients had been taking antibiotics for treatment of minor infections a few days prior to being hospitalized for salmonellosis. It is well-known that antibiotics can facilitate infection with resistant organisms because they inhibit sensitive bacterial flora of the host, enabling the invading resistant strains to gain a foothold and proliferate. Thus, individuals who harbor asymtomatic infection from antibiotic-resistant bacteria are at higher risk of gastrointestinal infection, since antibiotics are used commonly in therapeutic treatment for a variety of bacterial infections in the general population.

(c) Holmberg, Wells and Cohen Study

In a recently published paper,[3] Holmberg, Wells and Cohen of the Centers for Disease Control examined the origin and severity of antibiotic-resistant strains of bacteria responsible for 52 reported Salmonella outbreaks over a 12-year period. They report that multiple drug-resistant isolates have accounted for a steadily increasing percentage of human Salmonella infections and now represent approximately 20 to 30 percent of identified cases.[4] Because the increase of resistant bacteria is rapidly diminishing the effectiveness of doses for human use, there is a greater urgency for action to halt the proliferation of resistant bacteria. They reported, on the basis of epidemiological investigation, that of the 38 outbreaks of Salmonella infection from an identified source or mode of transmission, 69% of the resistant strains and 38% of the sensitive strains were of food-producing animal origin. The study also found that "[t]he case fatality rate for patients with identified infections with multiply resistant Salmonella was 4.2 percent, 21 times higher than the case fatality rate associated with antimicrobial-sensitive Salmonella infections."[5] The conjunction of the mortality rate for persons suffering from resistant Salmonella with the increasing frequency of resistant Salmonella make it urgent that action be taken to abate the spread of resistant bacteria.

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3 Holmberg, Wells and Cohen, Animal-to-Man Transmission of Antimicrobial-Resistant Salmonella: Investigations of U.S Outbreaks, 1971-1983, 225 Science 833 (1984).

4 Id.

5 Id.

3. Conclusion

There is overwhelming evidence to support withdrawal of subtherapeutic uses of penicillin and tetracyclines in animal feed. Therefore, the first criterion of suspension, the likelihood of withdrawal, is met.

B. Severity of Harm

The second criterion to be used in determining whether use of a drug constitutes an imminent hazard is the severity of the harm that could be caused by the product pending the completion of customary administrative proceedings to withdraw the product from the market.

On the basis of recent scientific evidence it can be established that hundreds of human deaths each year and several hundred deaths prior to the completion of withdrawal proceedings could result from subtherapeutic use of penicillin and the tetracyclines in animal feed.

It has been known for some time that subtherapeutic use of penicillin and tetracyclines in animal feed exerts selective pressure on animal bacterial populations, creating large reservoirs of strains of bacteria resistant to these and closely related antibiotics.[6] Salmonella bacteria resistant to one or more antibiotics are responsible for the majority of human deaths

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6 Sun, M., Use of Antibiotics in Animal Feed Challenged, 226 Science 144 (1984).

from Salmonella infection.[7] Dr. Holmberg's recent study shows that 64% of all multiply resistant Salmonella outbreaks in humans are traceable to animal sources, either animal-source food or live animals.[8] Given the selective pressure for the proliferation of resistant strains cited before, these findings clearly implicate subtherapeutic use of antibiotics in animal feed with human disease. In the discussion of likelihood of harm which follows, we discuss the number of deaths which could be associated with continued subtherapeutic use of these antibiotics in animal feed pending completion of withdrawal proceedings.

The less severe harm associated with nonfatal cases of infection with antibiotic-resistant strains of Salmonella should also be weighed in the imminent hazard determination. The resistance to antibiotics in these cases results in difficulty of treatment when indicated and consequently in longer duration of the illness and its symptoms. Further, there is evidence that treatment of other diseases with antibiotics may cause resistant Salmonella to predominate in an individual's system and result in the symptomatic expression of an otherwise asymptomatic infection.[9]

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7 Holmberg, supra, p. 10, 225 Science at 835.

8 Id. at 834.

9 Holmberg, supra p. 8, 311 New Eng. J. Med. 617.

C. Likelihood of Harm

The third component of the imminent hazard determination is the likelihood that the product will cause serious harm while the administrative process is being completed. The administrative process of withdrawal of the new animal drug approvals of penicillin and tetracyclines has already taken several years. Completion of this administrative process could take another three years.[10]

A preliminary risk analysis, outlined below, projects a mortality rate of between 100 and 300 deaths per year linked to subtherapeutic animal feed uses of penicillin and tetracyclines. In addition, over 2,700 reports of Salmonella cases and over 270,000 unreported cases of Salmonella infection may be associated on an annual basis with the use of penicillin and tetracyclines in animal feeds. These data demonstrate that there is a substantial likelihood of serious harm to the public health being caused while withdrawal proceedings are completed.

1. Estimated Annual Mortality Linked to Animals Fed Subtherapeutic Doses of Penicillin and Tetracyclines in Animal Feed

(a) Method 1

According to the Centers for Disease Control, approximately 40,000 cases of Salmonella infection in humans are reported each

10 Letter from Alair Townsend, Assistant Secretary for Management and Budget, HHS, to Hon. Jamie I. Whitten, Chairman, House Committee on Appropriations (June 23, 1981).

year in the United States.[11] Since 20-30% of Salmonella strains isolated from humans are resistant to one or more antibiotics,[12] a conservative estimate of the number of cases due to resistant strains of Salmonella bacteria is 8,000 (20%). Of these, an estimated 336 cases may be fatal, assuming a 4.2% fatality rate for resistant Salmonella infections.[13] Since 69% of reported Salmonella outbreaks involving antibiotic-resistant strains are traceable to animal sources, of the estimated 336 deaths from resistant bacteria 69%, or 232, are attributable to resistant bacteria from animal sources. Penicillin and tetracyclines constitute approximately 50% of all antibiotics produced in the United States.[14] We can assume that a similar proportion of penicillin and tetracyclines is used in the livestock industry (although the percentage may in fact be higher) since approximately half the antibiotics produced in the United States is

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11 Personal communication with Scott D. Holmberg, M.D., Enteric Diseases Branch, Centers for Disease Control, Atlanta, Georgia. This estimate is supported by the figure of 35,625 cases reported in 1981, up 10,000 from ten years earlier, reported by Riley, Importance of Host Factors in Human Salmonellosis Caused by Multiresistant Strains of Salmonella, 149 J. of Infectious Diseases at 878 (1980).

12 Holmberg, supra p.10, 225 Science at 833.

13 Id.

14 Personal communication with Edward Capeuchelli, Energy and Chemical Division, U.S. Trade Commission, Washington, D.C. In 1982, penicillin (9,507,000 lbs) and tetracycline (7,243,000 lbs) accounted for a total of 51.5% of the 32,518,000 lbs. of antibiotics produced in the U.S.

used in the animal livestock industry.[15] Next, since subtherapeutic antibiotic use constitutes most of all antibiotic use for animals, we assume that this use is responsible for virtually all antibiotic resistance among animal bacterial populations.[16] Thus, if half the resistant strains of Salmonella from animal sources have emerged under the selective pressure of subtherapeutic use of penicillin and tetracyclines, it is estimated that 116 (0.5 x 232) Salmonella deaths each year are associated with subtherapeutic use of these antibiotics.

(b) Method 2

An alternative method of risk estimate is based on the actual mortality incidence from Salmonella infections. According to statistics compiled by the Centers for Disease Control, between 1,000 and 1,500 deaths each year are associated with Salmonella outbreaks in the United States.[17] The recent Holmberg, et al., study indicates that 76.5% of all fatal

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15 National Academy of Sciences, The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds 7-8 (1980).

16 The remaining use of antibiotics in animals is for therapeutic treatment which is episodic in nature and of limited duration. It is reasonable to assume that such use does not contribute significantly, if at all, to the longterm, sustained development of antibiotic-resistant bacterial strains in animals.

17 Private communication with Scott D. Holmberg, M.D., Enteric Diseases Branch, Centers for Disease Control, Atlanta, Ga.

Salmonella infections are associated with resistant bacteria.[18] Application of this percentage to the lower estimate of 1,000 Salmonella fatalities per year gives an estimate of 756 deaths per year from resistant strains of Salmonella. As in the first method of analysis, the number of fatal resistant infections traceable to animal sources is estimated based on the finding that 69% of multiply resistant Salmonella outbreaks are traceable to animal sources, giving a figure of 528 deaths per year. As in the previous analysis, it is assumed that penicillin and tetracyclines constitute 50% of the antibiotics used subtherapeutically in animal feed and that virtually all antibiotic-resistant strains of Salmonella of animal origin are linked to subtherapeutic use of antibiotics in animal feed. Thus, an estimated one-half of the 528 fatalities from infections by resistant strains result from subtherapeutic use of penicillin and tetracyclines, or 264 deaths per year.

2. Estimated Annual Morbidity Linked to Animals Fed Subtherapeutic Doses of Penicillin and Tetracyclines in Animal Feed

Resistant strains of bacteria emerging in animal populations given subtherapeutic amounts of penicillin and tetracyclines in animal feed could be responsible for an estimated 270,000 nonfatal cases of Salmonella each year. In these 270,000 cases the

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18 Holmberg, supra p. 10, 225 Science 833-834. Holmberg found 13 deaths from 312 Salmonella cases associated with resistant bacteria and 4 deaths from 1,912 Salmonella cases associated with sensitive strains. Thus, out of a total of 2,224 cases, 13 out of 17 deaths, or 76.5% were associated with resistant Salmonella strains.

resistance of the bacteria to antibiotic treatment may increase the duration of the illness and its symptoms. This estimate is arrived at by means of the following analysis. Approximately 40,000 cases of Salmonella bacterial infection are reported each year.[19] An estimated 20% of these cases, or 8,000 cases, are infections by resistant strains of bacteria.[20] Of these estimated 8,000 reported cases of infection by resistant Salmonella, 69%, or 5,520, can be attributed to animal sources, and 50% or 2,760, of these are attributed to bacterial strains whose resistance is a result of subtherapeutic use of penicillin and tetracyclines in animal feeds.[21] Since only approximately 1% of all cases of Salmonella infection are clinically reported,[22] the 2,760 figure is multiplied by one hundred, giving an estimate of over 270,000 cases of non-fatal salmonellosis each year due to strains whose resistance is associated with the subtherapeutic use of penicillin and tetracyclines in animal feeds.

D. Risk To Human or Animal Health of Suspending Subtherapeutic Uses of Penicillin and Tetracyclines in Animal Feeds

The fourth criterion used in deciding whether an imminent hazard exists is the risk to the health of humans or animals that would result from the immediate removal of the drug. No significant risk would be associated with suspending approval of

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19 Supra, p. 13.

20 Supra, p. 14.

21 Id.

22 Private communication with Scott D. Holmberg, M.D., Enteric Branch, Centers for Disease Control, Atlanta, GA.

subtherapeutic uses of penicillin and tetracyclines in animal feed. No potential health risks to humans have been discussed in the literature. The health risk to animals can be greatly minimized, or even eliminated, by use of substitute antibiotics and better farming practices.

1. Risks to Animal Health

It has been claimed that subtherapeutic doses of antibiotics are fed to farm animals in order to (1) prevent disease outbreaks among livestock, (2) increase feed efficiency (weight gain per unit of food) and (3) promote growth.[23]

Withdrawing subtherapeutic uses of penicillin and tetracyclines would serve to eliminate these intended benefits. Decreased feed efficiency and slower growth are purely economic effects. They pose no health risks to the animals. The sole health risk to animals, then, is the hypothetical increased likelihood of disease. This risk is not severe, since diseased animals, whether or not they are already receiving low levels of antibiotics, are typically treated with therapeutic doses of antibiotics. NRDC is not advocating a ban on treatment of actual disease with antibiotics. Additionally, it is increasingly recognized by the livestock industry that antibiotics at any dose level do not treat infection caused by resistant organisms.

Two effective alternatives exist to minimize the incidence of illness among farm animals. The first and simplest alterna-

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23 Office of Technology Assessment, U.S. Congress, Drugs in Livestock Feed, Vol. I: Technical Rept. 5 (1979).

tive is for farmers to substitute other antibiotics for penicillin and tetracyclines in animal feeds. Alternative antibiotics currently used in animal feeds include bacitracin, nitrofurazone, banbermycin, novobiocin, monensin, tylosin and others.[24]

Though some have argued that the substitutes for penicillin and tetracyclines are not as effective, there is substantial evidence that they are effective. For example, tylosin and bacitracin are considered excellent substitutes for tetracyclines and penicillin in swine, chicken and turkeys.[25] In the case of pork and beef, tylosin and bacitracin are considered viable substitutes.[26]

Another method of reducing the incidence of disease in farm animals would involve altering farming practices. Intensive farming practice confines animals, usually with very little room for each animal, for most or all of their lives, and rigidly controls their diet, thereby altering their physical and behavioral characteristics. The confinement and crowding creates a great deal of stress for animals, and this stress increases the risk of disease. Since the animals are so crowded, disease spreads quickly. Many farmers who practice this type of animal

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24 Report of the Comptroller General of the United States, U.S. General Accounting Office: Need To Establish Safety And Effectiveness of Antibiotics Used In Animal Feeds 4 (1977). Haysten, I. et al., Effect of Banbermycin and Tylosin on Performance of Growing-Finishing Swine, 50 J. Animal Sciences 484 (1980).

25 Headley, J.C., Economic Aspects of Drug and Chemical Additives, p. 30, paper commissioned for OTA study, supra, p. 1d.

26 Id.

husbandry may feel that it is necessary to administer subtherapeutic doses of antibiotics in order to counteract these disease-producing and disease-spreading influences. Even so, death losses have increased due to confinement systems, at least in hog farming,[27] and this can often be attributed to bacterial resistance to antibiotics being used in a futile attempt to control infections.

Non-intensively farmed animals are not confined as much, may have access to the outdoors and are weaned later. Each of these practices lessens the stress on the animals. This type of farming is relatively low cost, since the farmer need not buy the expensive facilities and equipment needed by the confinement farmer.[28]

Finally, unsanitary conditions cause the animals to be even more stressed, and antibiotic need is, therefore, greater. Only a small number of farms may actually have these conditions, but there is concern that some use of antibiotics may be covering up for bad practices.[29] In these cases, better sanitation could minimize the animal health risk posed by removal of antibiotics.

For farms with less intensive animal-raising practices and good management, subtherapeutic levels of antibiotics may not be

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27 Statement of Charles Henry Hassebrook, Center for Rural Affairs, Walthill, Nebraska, before the House Committee on Interstate and Foreign Commerce, Subcommittee on Health and the Environment, Serial No. 96-169, June 12 and 24, 1980.

28 Id.

29 Green, Feed Additives: A Crutch for Poor Management? Feedstuffs, Feb. 18, 1980, 36.

necessary. If they can still decrease the extent of disease, then effective substitutes for penicillin and tetracyclines are available. NRDC is, therefore, convinced that there is no significant health risk to animals associated with banning subtherapeutic doses of penicillin and tetracyclines from animal feed. On the contrary, there is a positive benefit, since if the animals should become ill, there is at least the chance of treating them if the causative agent is a sensitive bacterial strain.

In conclusion, the risk to animal health from suspension is not as severe nor as important as the human health risk from continued application of these antibiotics in animal feed.

2. Risks To Human Health

NRDC has found no evidence or even suggestions in the medical and public health literature that withdrawal of penicillin and tetracyclines from subtherapeutic uses in animal feeds would result in risks to human health. The only effect on humans would be economic. A number of studies have modelled production and prices of meat if various combinations of antibiotics are banned from animal feed. Results indicate that economic losses to consumers will be felt mostly in the first few

years of a ban[30] and that, over the longer term, use of existing alternatives to these antibiotics would substantially mitigate the economic effects on consumers.[31]

Since the average citizen consumes almost three times the amount of meat per year that the U.S. Department of Agriculture considers necessary to meet nutritional standards,[32] the difference of a few less pounds of meat or a few extra dollars per year per person cannot be considered a human health risk. Economic hardship may be felt by the low-income members of society, but no evidence suggests that this presents a health problem, given the fact that most food prices will not be affected by a ban, and the impact of slightly nigher meat prices is, for the most part, temporary.

A conceivable risk to human health could be that of eating meat from an animal which became ill as a result of withdrawing subtherapeutic use of penicillin and tetracyclines. First, using alternate antibiotics and improved farming practices, a farmer can control disease in the great majority of animals. If an animal does become ill, the farmer can treat the animal with therapeutic doses of antibiotics, a standard practice whose effectiveness would actually be increased by the proposed ban.

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30 U.S. Dept. of Agriculture, Economic Effects of a Prohibition on the Use of Selected Animal Drugs 2 (1978).

31 Headley, supra p. 19, at 30-31.

32 Council for Agricultural Science and Technology, Antibiotics in Animal Feeds 34 (1981).

E. The Availability of Other Approaches to Protect the Public Health

The fifth and final criterion for a finding of imminent hazard is the lack of other suitable approaches to protect the public.

NRDC has found no mention in the literature of effective alternatives, or, indeed, any alternatives to protect the public health other than a ban on subtherapeutic uses of penicillin and tetracyclines in animal feed. While the only conceivable possibility would be an extensive public education campaign on careful food and meat handling, this approach presents a number of difficulties. First, developing and implementing a large-scale education program would be more time consuming and less effective than an immediate ban in preventing unnecesary deaths and illness. Second, antibiotic-resistant bacteria, like other bacteria, can be transferred from animals to humans without the humans having direct contact with the animals. Humans can contract bacteria from utensils and kitchen counters that were at one point in contact with the animal or its by-products, such as the raw meat. Therefore, even careful handling of meat would be unlikely to eliminate completely the risk of bacterial transfer from animals to humans. Finally, a public education program would be expensive and resource-intensive, cancelling out some of the economic arguments against banning subtherapeutic uses of penicillin and tetracyclines in animal feed. NRDC concludes that a public education campaign would be an unsatisfactory option, leaving no alternative to a ban.

III. CONCLUSION

In view of the likelihood that FDA will utlimately withdraw approval, the severe harm that is likely to occur pending completion of withdrawal proceedings, the insignificant risk to human or animal health from suspension and the lack of effective alternatives to protect the public health, NRDC respectfully requests that you act immediately to suspend approval of subtherapeutic use of penicillin and tetracyclines in animal feeds.

Respectfully submitted,

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The undersigned certify that, to the best of their knowledge and belief, this petition includes all data and information on which the petition relies, and that it includes representative data and information known to the petitioners that are unfavorable to the petition.

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Drugs in Livestock Feed

Volume I: Technical Report

OTA CONGRESS OF THE UNITED STATES

BENEFITS

The benefits of using antibacterials in animal feeds are:

- The prevention of disease,
- The promotion of growth, and
- The improvement of feed efficiency.

The evidence points to the disease-prevention effect as being primarily responsible for increased weight gain.

While increased weight gain resulting from low doses of antibacterials and DES is not in dispute, the amount of gain is. Even though drugs may increase weight gain by only a few percentage points, the absolute increase is large because of the size of the livestock market.

Present levels of livestock production do not depend specifically on the use of DES and the addition of low levels of tetracyclines, penicillins, sulfa, and nitrofurans to feeds because substitute drugs are available. In addition, if adopted, the current Food and Drug Administration (FDA) proposal to restrict but not totally ban the most widely used antibiotic, tetracycline, could mitigate the impact of banning or restricting other drugs used for this purpose.

The economic consequences of such decisions, however, are a separate matter because marginal increases or decreases in production may make the critical difference in the profitability of the livestock industry. Economic dislocations within subsectors of the livestock market could be significant over the short term. Such economic effects are often raised in objections to proposed changes in regulations, but present statutory authority limits FDA's decisionary basis to scientific evidence of effectiveness and safety. Although under present law FDA does consider the practicality of achieving the desired result of regulatory changes, FDA does not explicitly consider the economic consequences of these changes. When FDA's proposed regulations have been successfully challenged, it has usually been on the grounds that FDA's procedures, rather than the substance of the law, were faulty.

There may soon be an opportunity to observe whether or not the banning of antibacterials will result in significant changes in production. FDA has withdrawn approval of one of the four nitrofurans, an antibacterial originally approved for food animal use, and will soon enter hearings on the remaining approvals. One of these, furazolidone, is the most widely used. Predictions point to no effect on beef and pork production but to significant short-term effects on poultry production. (See tables 23 and 24.) Penicillin and tetracyclines are also widely used in poultry, and their uses overlap extensively with the nitrofurans. (See tables 1, 2, 4, 5, and 9.) Even if penicillin were banned subsequently, tetracycline would remain available, since FDA's proposal would allow its continued use if alternatives were unavailable. If these antibacterials cannot replace nitrofurans, effects should be observed immediately.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Washington, D.C.

6/23/81

Honorable Jamie L. Whitten
Chairman
Committee on Appropriations
House of Representatives
Washington, D.C. 20515

Dear Mr. Whitten:

As you know, in its report on FDA's FY 1981 Appropriation Bill, the Committee earmarked $1.5 million to be spent for research to generate new information relative to the possible hazards to human health from the subtherapeutic use of antibiotics in animal feeds. No additional funds were added to FDA's appropriation for this purpose, however. This letter is intended to apprise you of our progress in this regard, and ask your concurrence in our planned use of funds currently reserved for this purpose.

Last year, in response to requested guidance on this subject, the National Academy of Sciences (NAS) concluded that "a comprehensive, all-encompassing study could not be realized or even approximated because of insurmountable technical difficulties." Instead, NAS recommended a "sequence of studies on individual aspects of the transmission chain" for antibiotic resistance.

Now, after a great deal of study and with the scientific advice of experts in this field from outside FDA (i.e., the National Institutes of Health, Centers for Disease Control, United Kingdom, the Netherlands) it has been determined that a reasonable level of research appropriate to this issue can be done with about one-half of the $1.5 million originally earmarked for this purpose. The studies that FDA proposes undertaking will require two to three years to complete and evaluate, and it is possible that these studies may lead only to indications of the need for further research. If further studies are not necessary upon completion of the presently planned research, and if FDA decides to proceed with regulatory action to prohibit the use of low levels of antibiotics in animal feed, the procedures we would be required to follow would probably consume at least another three years after the completion of the research.

We are convinced that our current approach to the research that we have been directed to do is most advisable, and will accomplish all that can be done at this time. This will leave unobligated $750,000 of the originally earmarked $1.5 million. With your approval, FDA proposes that this amount be included as part of the $10.5 million that FDA has been directed to save in this year's revised budget allowance.

If you desire we will be glad to provide any specifics regarding our planned research, or any other information you might need in consideration of this information.

Sincerely yours,

/s/

Alair Townsend
Assistant Secretary for
Management and Budget

cc: Senator Thad Cochran
Mr. Stephen Kohashi

THE ECONOMIC EFFECTS OF A PROHIBITION ON THE USE OF SELECTED ANIMAL DRUGS

U.S. DEPARTMENT OF AGRICULTURE
Economics, Statistics and Cooperatives Service
September 1978

EXECUTIVE SUMMARY

The Economic Effects of a Prohibition on the Use of Selected Animal Drugs

INTRODUCTION

Since earliest times man has struggled to develop an abundant and safe food supply. Over time, though, the increased use of chemicals and drugs has played an important part in improving man's ability to increase production, retard spoilage and preserve in other ways the naturally perishable food substances.

These improvements have not come without a cost. Chemicals, once thought to be absolutely necessary for food preservation, are now being implicated as causal agents directly related to human health conditions. As a result, and in an attempt to protect the inherent safety of the food supply, public policies to ban or otherwise regulate the use of a wide variety of animal feed additives are being proposed and debated.

The subtherapeutic uses of some animal drugs are being questioned because of evidence linking resistant strains of certain organisms to the chronic intake of antibiotics. For example, the Food and Drug Administration (FDA) has demonstrated that strains Pasteurella multocida and Pasteurella haemolytica have developed a resistance to penicillin, streptomycin, sulfonamides and tetracyclines. The development of such resistance, is a serious concern because it makes the use of these antibiotics potentially less effective in dealing with human health problems.

Proposals to restrict the therapeutic and subtherapeutic use of the nitrofurans stem from the finding that these antibacterials produce tumors in laboratory animals. Since manufacturers have been unable to produce an adequate method of analysis to assure the absence of residues in human food, there continues to be doubts whether their use in animal feeds poses a threat to human health.

A potential proposal to restrict the use of sulfamethazine in hog feeding stems from the continued high levels of sulfa residue being detected in pork tissue.

Farmers have used drugs at subtherapeutic levels in raising animals for approximately 25 years. Over the years they have come to believe that such a use (a) reduces the risk of animal disease outbreaks, (b) improves feed efficiency, and (c) reduces condemnations of the final product. In short, while limited scientific evidence is available to either support or refute the notion, the subtherapeutic use of animal drugs is now believed responsible for reducing the unit costs of animal production.

At the request of the United States Senate Committee on Agriculture, Nutrition, and Forestry, USDA initiated this study of the economic consequences of the proposed and potential retrictions on animal drug use. The study focused mainly on the effects such a restriction would have on food availability, food and farm prices, farm production costs, and the level and distribution of farm income.

While the results of this study must be considered as merely suggestive, they do indicate that the economic system would generally be quite resilient to a more restrictive policy on animal drug use. Costs of production, and therefore consumer prices, would increase initially but because the farm-level demand for most livestock products is inelastic, farm prices would increase more than proportionally. As a result, total net revenue to farmers would be initially enhanced. The increased profitability would encourage farmers to expand output in subsequent years and by the fifth year following the restriction on animal drug use, production and prices of most affected species would recover to approximately their baseline levels.

These results do not take into account any changes in the structure of production agriculture that might accompany an animal drug ban. Increased risks associated with feeding poultry and livestock in confinement without the low-level use of animal drugs could make such confinement production systems less viable and change the magnitude of this result. On the other hand, we were not able to measure the effect of changes in management practices that might occur in anticipation of or following the enactment of such a rule. Improved sanitation and pasture rotation could reduce the magnitude of even the first year affects as we have shown them.

The Study

Basic science data are essential to a study such as this. Without good data on the effects of subtherapeutic drug use on feed efficiency, growth rates, mortality and product condemnation rates, it is impossible to develop precise estimates of the economic effects resulting from a ban. The basic science data for this study were obtained from USDA and Land Grant university scientists, veterinarians, others in private business, and professional journals. Most estimates were extrapolated from small scale test results since other data were not available. Most of the data were from tests conducted when the additives were first introduced in the 1950's and 1960's. In many instances there were wide variations in test results making estimates of the changes in production coefficients subject to error. Despite such difficulties, however, it should be emphasized that the best available scientific data were used for this study.

Because the available scientific evidence on the animal production effects of drug use are not conclusive, two levels of drug efficacy were assumed--a moderate and high level. Such a procedure, therefore, provides a range of potential outcomes that likely bracket what could reasonably be expected to occur in reality.

The estimated initial effects on animal production of restrictions on the low-level use of selected animal drugs are shown in Table 1. These data indicate, for example, that the first year cumulative effect of a restriction on the use tetracyclines and sulfa in feeding hogs would be a 4.9 to 17.8 percent reduction in output, depending on what is assumed about drug efficacy.

As the data indicate, use of animal drugs within the same specie was assumed to generate additive effects. That is, banning the use of all four animal drugs was assumed to be equivalent to the cumulative effect of separate bans occurring one at a time. It was also assumed that substitute drugs would not be available for use and that producers would not change management practices in order to effectively circumvent the regulations. While these assumptions admittedly do not mirror what would take place in the real world they make the problem amenable to analysis and allow us to set bounds on the extent of the economic impact.

The economic analysis was conducted assuming both a species-by-species ban of each animal drug and an across species concurrent ban of all the drugs. The cummulative effects of an across species ban were estimated by taking into account the adjustments in production that would occur as a result of cross-commodity effects. For example, the increased demand for beef resulting from higher pork prices was explicitly taken into account. The net effects of an animal drug ban on prices, production and consumption were traced for a hypothetical 5 year period following the ban to indicate whether, and to what extent, there would be long term adjustments to the changed conditions.

Results 1/

The study results indicate that, at least initially, net farm income, farm and food prices, and farm production costs would all increase if the subtherapeutic use of animal drugs were restricted. Farm production costs per unit would increase because animal production is made less feed efficient and because mortality is increased. Farm and food prices would increase because fewer animal units are offered for sale. Net farm income would increase because increases in aggregate costs of production would be than offset by increases in aggregate receipts. This result would, of course, be expected in cases where the demand for a product is relatively price inelastic.

1/ In order to simplify the discussion only the effects of the moderate efficacy assumption are explicitly discussed in this summary. If the high efficacy response is assumed, the pattern of adjustment is identical to that assuming moderate efficacy. However, reductions in output for the affected specie are more pronounced and, as a result, prices are relatively higher. Magnitude changes are shown in the tables attached.

Total net farm income in the first year following the animal drug ban would be about $1.2 billion above the baseline estimate (moderate efficacy). Increases in livestock cash receipts (+2.9%) would more than offset the relatively small decreases in cash receipts from crops (-1.4%). In subsequent years, net farm income would move steadily closer to the baseline estimate. By the fourth period, net farm income would be slightly below the baseline estimate (-1.2%) reflecting primarily the somewhat higher costs of producing about the same total output of livestock product. (Table 2)

Consumer price impacts follow essentially the same pattern as the index of farm prices received. The first year impact on the CPI for food is the most significant (1.2 percent above the baseline estimate). Consumer prices for the livestock products would be affected most. Retail poultry prices would be up 10 percent, beef prices up 3 percent and pork prices up about 4 percent. By the fifth period, slightly higher prices would persist for pork and poultry products, but because of the relatively low weight of these items in the food CPI, there would be almost no change from the baseline food CPI estimate. (Table 3)

Under the assumption of moderate drug efficacy, a restriction on animal drug use implies about a 7 pound per person reduction in the availability of red meat and poultry products. Broiler consumption in the first year is reduced most (3 1/2 pounds per capita); followed by pork (2.8 pounds), turkeys (1/2 pound) and beef (1/4 pound). (Table 4)

Price deviations from the base estimate for both the moderate and high level efficacy are shown in Table 5. In the first year, broiler and turkey prices would be above the baseline estimate by about 12 percent, assuming moderate efficacy. Barrow and gilt prices would be up about 5 percent and fed beef prices would be about 4 percent above the baseline estimate.

By the fifth year, all prices would be relatively closer to the baseline estimates. Broiler and turkey prices would still be higher than baseline reflecting the relatively higher costs of producing poultry products without the subtherapeutic use of the chemicals and drugs.

The study also provides an estimate of the effects of a ban on the use of the four additives in producing dairy products and sheep. The impact of such a ban on dairy producers would be minimal. Such additives are now used at subtherapeutic levels only in the feeding of calves. Study results indicate that costs of producing milk would increase less than 1 cent per cwt. if that use were banned.

Impacts of an animal drug ban on sheep and lamb production would also be minimal. Study results indicate an approximate 1 percent reduction in gross farm receipts to sheep producers if the additives had been banned in 1976. In that year consumers would have paid about a cent per pound more for mutton and lamb and there would have been about 47,000 cwt. less meat available.

Table 1—Estimated Percentage Change in Livestock Product Output from Banning Selected Drugs in Subtherapeutic Uses, Moderate and High Drug Efficacy, Each Species Considered Separately, First Period (1976)[1]

Animal species	Penicillin		Tetracyclines		Nitrofurans[2]		Sulfa[3]		Cumulative effect	
	Drug Efficacy									
	Moderate	High	Moderate	High	Moderate	High	Moderate	High	Moderate	High
	Percent									
Fed beef cattle	--	--	-0.4	-0.8	--	--	--	--	-0.4	-0.8
Hogs	--	--	-3.4	-15.6	--	--	-1.5	-2.2	-4.9	-17.8
Broilers	-2.1	-3.8	-6.4	-11.5	0.2	-5.7	--	--	-8.3	-21.0
Egg production	-0.6	-1.0	-1.2	-2.3	0.1	-0.3	--	--	-1.7	-3.6
Turkeys	-1.4	-2.8	-2.8	-4.6	-1.9	-8.7	--	--	-6.1	-16.1

[1]The higher the expected response to a feed additive, the greater will be the reduction in output if the additive is banned.

[2]In poultry, it is possible to get a slight increase in output when nitrofurans are removed from the feed. These circumstances are explained in the appendix material on poultry. A ban on nitrofurans at all levels was assumed.

[3]The major effect would be from the sulfa drugs but would also include the effects attributed to penicillin and the nitrofurans.

Table 2--Percent Deviation from Base Projections of Selected Farm Income Indicators Resulting from a Ban on the Subtherapeutic Use of Animal Drugs, Moderate and High Efficacy

	Period 1		Period 2		Period 3		Period 4		Period 5	
	Moderate	High	Moderate	High	Moderate	High	Moderate	High	Moderate	High
Cash receipts from livestock	2.9	6.7	2.0	5.2	1.5	3.1	0.9	1.7	0.5	1.3
Cattle	3.0	11.3	2.3	8.3	2.0	5.0	1.2	2.4	0.4	1.8
Hogs	0.2	- 3.5	-0.1	- 2.6	-0.0	- 1.3	0.2	- 0.2	0.2	0.0
Broilers	8.4	19.1	5.9	-18.3	5.5	12.2	3.9	8.9	2.9	6.2
Turkeys	2.1	1.6	1.0	1.6	0.4	1.1	0.4	0.8	0.5	1.1
Cash receipts from all crops	-1.4	3.4	-1.1	-2.0	-0.6	-1.1	- .6	-0.9	-0.4	-0.7
Corn	-3.4	- 8.9	-2.7	-3.8	-1.5	-2.4	-1.2	-1.6	-1.0	-1.5
Soybeans	-3.0	- 7.2	-3.0	-5.1	-1.9	-3.7	-1.3	-2.6	-1.1	-1.9
Oil crops	-2.7	-.6.7	-2.8	-4.8	-1.2	-3.4	-1.3	-2.4	-1.0	-1.8
Total receipts from marketings	0.9	2.7	0.5	1.9	0.5	1.1	0.3	0.5	0.1	0.4
Total farm expenses	-0.2	- 0.4	0.3	0.5	0.4	1.0	0.5	1.0	0.5	1.2
Total net farm income	4.7	10.9	1.6	6.6	0.0	1.2	-1.2	-2.0	-2.1	-3.8

Table 3--Percent Deviations from Base Projections of Selected Consumer Price Indexes, Animal Drug Ban, Moderate and High Efficacy

	Period 1		Period 2		Period 3		Period 4		Period 5	
	Moderate	High	Moderate	High	Moderate	High	Moderate	High	Moderate	High
Beef and veal	2.7	10.4	2.2	7.7	1.4	3.4	0.7	1.4	0.0	0.7
Pork	4.5	14.7	3.5	11.8	2.1	7.3	1.4	4.8	1.0	3.2
All red meats	3.2	11.7	2.6	8.9	1.6	4.6	.9	2.4	0.3	1.4
Poultry	10.3	27.6	5.7	15.9	2.6	7.4	2.4	6.5	2.2	5.6
Total, meat, poultry and fish	3.4	11.0	2.4	7.7	1.3	3.9	0.9	2.3	0.5	1.6
Total livestock and products	2.6	8.1	1.8	7.1	1.0	2.8	0.6	1.6	0.3	1.2
Food at home CPI	1.2	3.8	0.9	2.7	0.4	1.3	0.3	0.7	0.2	0.6
Total CPI	0.2	0.5	0.1	0.3	0.1	0.2	0.04	0.1	0.0	0.04

Table 3--Percent Deviations from Base Projections of Selected Consumer Price Indexes, Animal Drug Ban, Moderate and High Efficacy

	Period 1		Period 2		Period 3		Period 4		Period 5	
	Moderate	High	Moderate	High	Moderate	High	Moderate	High	Moderate	High
Beef and veal	2.7	10.4	2.2	7.7	1.4	3.4	0.7	1.4	0.0	0.7
Pork	4.5	14.7	3.5	11.8	2.1	7.3	1.4	4.8	1.0	3.2
All red meats	3.2	11.7	2.6	8.9	1.6	4.6	.9	2.4	0.3	1.4
Poultry	10.3	27.6	5.7	15.9	2.6	7.4	2.4	6.5	2.2	5.6
Total, meat, poultry and fish	3.4	11.0	2.4	7.7	1.3	3.9	0.9	2.3	0.5	1.6
Total livestock and products	2.6	8.1	1.8	7.1	1.0	2.8	0.6	1.6	0.3	1.2
Food at home CPI	1.2	3.8	0.9	2.7	0.4	1.3	0.3	0.7	0.2	0.6
Total CPI	0.2	0.5	0.1	0.3	0.1	0.2	0.04	0.1	0.0	0.04

Table 4 -- Estimated Quantity and Percentage Change in Per Capita Production of Beef, Pork, Broilers and Turkeys from Base from Ban on the Subtherapeutic Use of Animal Drugs 1/

	Units	Drug efficacy			
		Moderate		High	
		Period 1	Period 5	Period 1	Period 5
All beef (carcass wt.)	lbs.	- .23	+ .39	- .34	+ .72
Percentage change	Pct.	- .21	+ .36	- .31	+ .67
Pork (carcass wt.)	lbs.	-2.79	- .58	-10.25	-2.10
Percentage change	Pct.	-4.52	-0.85	-16.59	-3.08
Broilers (RTC) 2/	lbs.	-3.44	- .89	- 8.70	-2.26
Percentage change	Pct.	-7.26	-1.61	-18.37	-4.08
Turkeys (RTC) 2/	lbs.	- .59	- .28	- 1.45	- .70
Percentage change	Pct.	-5.94	-2.50	-14.60	-6.26
Total net change	lbs.	-7.05	-1.36	-20.74	-4.34
Percentage change	Pct.	-3.06	- .56	- 9.01	-1.79

1/ Based on 1977 civilian population of 214.7 million.
2/ RTC = "ready to cook."

Table 5--Price Deviations from Base Projections, Resulting from a Ban on the Subtherapeutic Use of Selected Animal Drugs, Moderate and High Efficacy. 1/

	Units	Years				
		1	2	3	4	5
		Moderate Efficacy				
Barrows and gilts (liveweight prices)	$/cwt.	2.32	1.62	1.11	.72	.54
Percentage change	Pct.	5.02	3.83	2.34	1.59	1.14
Broilers (RTC wholesale price)[2]	¢/lb.	5.03	2.75	1.77	1.46	1.34
Percentage change	Pct.	12.99	6.94	3.09	2.67	2.25
Turkeys (liveweight farm prices)	¢/lb.	3.39	1.90	1.32	1.19	1.19
Percentage change	Pct.	11.61	6.70	3.42	3.51	3.54
Fed beef (steer price, Omaha)	$/cwt.	1.68	1.33	1.06	.60	0
Percentage change	Pct.	4.30	3.30	2.00	1.00	0
		High Efficacy				
Barrows and gilts (liveweight prices)	$/cwt.	7.45	5.49	3.80	2.37	1.67
Percentage change	Pct.	16.13	12.97	8.00	5.24	3.53
Broilers (RTC wholesale price)[2]	¢/lb.	13.80	7.91	5.15	4.08	3.60
Percentage change	Pct.	35.65	20.00	8.98	7.46	6.04
Turkeys (liveweight farm price)	¢/lb.	7.49	4.66	3.43	2.98	2.98
Percentage change	Pct.	25.64	16.42	8.88	8.79	8.88
Fed beef (steer price, Omaha)	$/cwt.	6.02	4.55	2.65	1.20	.60
Percentage change	Pct.	15.34	11.27	5.03	2.00	.96

[1]Drugs considered banned were penicillin, tetracyclines and sulfa at subtherapeutic levels and nitrofurans at all levels.

[2]RTC = "ready to cook."

Statement of
Charles Henry Hassebrook
Center for Rural Affairs
Walthill, Nebraska

before the

House Subcommittee on Interstate and Foreign Commerce
Subcommittee on Health and Environment

The Center for Rural Affairs is a non-profit, unaffiliated organization based in Walthill, Nebraska. We have monitored structural change in the hog production industry since 1974 when we published the first verion of our report "Who Will Sit Up With the Corporate Sow?". We recently published our fourth update of that report in addition to numerous reports on the role of public policy in fostering concentration in the hog industry. We appreciate the invitation to discuss the impact of restrictions on subtherapeutic antibiotic use on the structure of the hog industry. However, we take no position on this legislation. Its merit must be decided on a range of questions much broader than structural impacts, to which we will limit our comments.

Many more hog producers are threatened by restructuring in the direction of greater concentration, than are threatened by potential dispersion stimulated by limitations on antibiotic use. In fact, restricting antibiotic use would likely minimize structural change and displacement, by preventing concentration in very antibiotic-dependent large scale units. The majority of hogs are still produced by relatively small and moderate sized farms which could adapt to antibiotic restrictions. However, that adaptability and smaller producers may not survive long given a continuation of current trends.

STRUCTURAL CHANGE IN THE HOG PRODUCTION INDUSTRY

The hog industry is in the midst of rapid structural change. The number of hog producers has declined by 80 percent in the last 30 years. USDA

predicts a decline of 80 percent in the number of pork producers in just 20 years. (Van Arsdall). Our research in Nebraska has disclosed a rapid trend toward a non-family farm structure. In 1974 approximately 7% of the state's feeder pig crop was produced in corporate or cooperative hog factories, owned by groups of farm and non-farm investors and operated by employees. By 1979 that share had mushroomed to nearly one fourth. Last year, growth among the largest four percent of the nation's hog producers accounted for over two thirds of the dramatic growth in hog numbers which has glutted the market forcing prices to less than half of their recent highs. This condition will be corrected only by the departure of a significant number of producers from the industry. This structural change has been made possible by confinement production techniques, a key component of which is subtherapeutic antibiotic use.

WHAT IS CONFINEMENT TECHNOLOGY AND HOW IS IT RELATED TO SUBTHERAPEUTIC ANTIBIOTIC USE?

Confinement hog production refers to a system in which hogs are confined within facilities for the entire production process. These systems are generally of a much larger than average scale and are equipped with modern labor-saving features.

Subtherapeutic antibiotic use is generally considered the key technological breakthrough making large scale confinement hog production possible. To quote the scientific community:

> "Action that would ban or restrict usage of antibiotics represents one of the few factors that would inhibit trends toward larger and more industrialized hog units."
> Technology Assessment of Integration of the Hog-Pork Industry
> National Science Foundation - July 8, 1977
>
> "The economics of producing swine and poultry in large confinement units is generally considered strongly dependent on prophylactic feeding of antibiotics to control diseases."
> Use of Antibiotics in Animal Feeds
> An interim summary presented to the Food and Drug Administration by the Council on Agricultural Science and Technology (CAST)

Putting a large number of animals in a single production unit exposes producers to the risk of enormous losses, should a disease gain a foothold and spread through the entire herd. The high cost of confinement facilities requires a higher degree of crowding to achieve the volume necessary to justify the investment. Higher crowding means higher stress and higher disease risk. Large scale confinement producers generally use early weaning systems, in which baby pigs are removed from their mothers at an early age. This technique allows more litters to be passed through a facility in a given time, allowing the necessary volume to justify the high cost of confinement facilities. Early weaning exposes baby pigs to weaning stress at a younger weaker age and deprives pigs of the natural antibodies contained in their mothers' milk, thus requiring antibiotic additives. The confinement technique of passing as many litters as possible through a single facility also increases the need for antibiotics by providing a steady supply of vulnerable young pigs in which diseases can remain alive and multiply. Even with current antibiotic use, large scale confinement systems have brought higher death losses to the hog industry ("Hogs", Another Revolution in U.S. Farming?, USDA).

IMPACT ON STRUCTURAL CHANGE

The entrance of new large scale producers to the hog industry would likely be impeded by the proposed restrictions. Existing large scale producers would probably reduce production. Efforts to reduce disease risk by limiting crowding and weaning pigs at older ages would reduce facility capacity. The degree of these impacts would be affected by the availability of substitutes.

Concern has been raised that restrictions on subtherapeutic antibiotic use could cause a major restructuring of the hog industry, back to very small

inefficient units producing only seasonally on pasture, resulting in irregular supplies of market hogs to packers and pork to consumers. We find no basis for these concerns.

Sixty percent of the nation's hogs are still produced in units marketing fewer than 1,000 head per year. Generally, these producers are not using total confinement facilities. Although many of these small and moderate scale producers are currently feeding antibiotics, they could effectively adapt to restrictions.

Irregular seasonal pork production is not the only alternative to large scale confinement hog production. A large part of the nation's pig crop comes from small and moderate scale producers using barns in which pigs are produced year round. These generally are older facilities, of which there is a surplus in farm areas, available at a very low opportunity cost. Although such facilities can not be well adapted to large scale production, they are appropriate to smaller producers and could be used effectively without subtherapeutic antibiotic use. Their low cost makes antibiotic-dependent crowding and early weaning unnecessary and uneconomical.

IMPACT ON PRODUCTION EFFICIENCY

We see no basis for the claim that the small and moderate scale producers whose position would be preserved by antibiotic restrictions are less efficient than large scale producers and costly to consumers.

To quote Secretary of Agriculture Bergland, "The most efficient hog producer today is not some guy who's got a $300,000 modern, sophisticated apparatus. . . . The most efficient in terms of cost is the guy who's sitting out there with an old fashioned system that's all paid for." (Newsweek, June 2, 1980). The only efficiency enjoyed by the large scale operations is in labor use, hardly a priority in a nation with persistent unemployment problems. This comes at the cost of energy intensiveness, a serious problem in a world

facing scarce and uncertain energy supplies. The primary force behind the rapid concentration in the hog industry is not economies of scale, but income tax subsidies which return high income investors up to 80 percent of their confinement facility investment in tax savings. Economic impact analyses which assign increased pork prices to the structural impact of antibiotic restrictions, should be re-examined.

SOCIAL IMPACTS

Preservation of opportunity for small and moderate scale hog production would have substantial positive impacts on rural communities. Because of the low investment, high labor nature of smaller hog production systems, they have been the opportunity crop for the non wealthy farmers. Hog production has been the first step on the ladder of farm success, enabling the small and beginning farmer to build equity, establish himself in farming, and purchase land. If the hog industry becomes concentrated, dispersed land ownership will receive a blow. Farm opportunity would become even more limited to a select few of wealthy farmers.

Secretary of Agriculture Bob Bergland has publicly recognized the costs of continuing the trend toward large scale food production. In an address calling for a national dialogue on the future structure of agriculture Bergland noted "With the decline in the number of farms and the number of farm people, we've seen a deterioration of many rural communities. . . . A distortion has taken place in the traditional rural social order. Something has been lost. Something of lasting worth.

This impact will be felt beyond the farm sector. The landmark study, Agribusiness and the Rural Community, often called the Arvin - Dinuba study after the two California communities on which it was based, reveals the positive impact on rural communities of dispersed farm ownership. The study

compared two communities, strikingly similiar in most characteristics except that one was economically based on large scale agriculture and the other on more modest sized operations. The small farm community supported significantly more businesses and people at a higher standard of living than did the large farm community. The small farm community had more and superior, community facilities and institutions and was governed in a more democratic manner.

SUMMARY

We foresee no adverse structural impact on the hog production industry from the limitations on subtherapeutic antibiotic use proposed in this legislation. Although such action would cause hardships for large antibiotic dependent producers, its overall impact would be to prevent a major restructuring and preserve economic opportunity for the small and moderate scale segment of the hog industry. By preserving economic opportunity for these farmers, antiobiotic restrictions would likely have a secondary impact of enhancing the economic and social vitality of country towns and rural communties.

CAST

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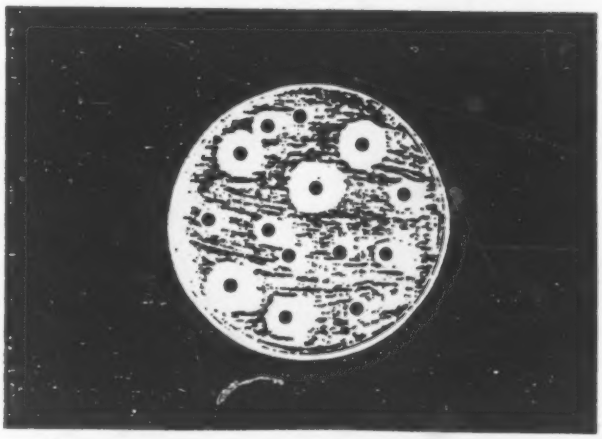
ANTIBIOTICS IN ANIMAL FEEDS



Council for
Agricultural Science and Technology
Report No. 88
March 1981

SOCIOECONOMIC IMPLICATIONS OF ANTIBIOTIC USAGE IN LIVESTOCK PRODUCTION

Banning the use of antibiotics in livestock feed would have some effect on the price and supply of meat. To the extent that meat prices would rise, we must determine how much more we would be willing to pay for meat in an attempt to protect the long-run effectiveness of antibiotics for treating humans and animals.

In an analysis by Headley (1978), presumably based on 1977 dollars, banning the use of tetracyclines and penicillin (without substitutes) as feed additives was estimated to result in an increase of $22.80 in annual cost of meat for a family of four. The impact of higher meat prices would be more severe for lower income families who spend a much larger proportion of their disposable family income for food, than it would be for richer families. Although the average American family spends about 17% of its disposable income for food, low-income families spend one-third of their disposable family income for food. Undoubtedly, low-income families would reduce their meat expenditures. The size of this reduction is very difficult to predict.

However, the Thrifty Food Plan (developed by US DA's Agricultural Research) which serves as the basis for determining Food Stamp eligibility suggests that the average citizen consumes more meat than is necessary to meet recommended nutritional levels. Thus, the Thrifty Food Plan recommends an annual consumption of 90 pounds of meat (69 pounds of red meat and 21 pounds of poultry) per person instead of the current average consumption of 245 pounds. Under the plan, the increase in the annual meat cost for the four-member, low-income family would be less than $10.

Risk And Uncertainty

Writing in the 1920s, Knight (1921) distinguished between risk and uncertainty. He said that risk exists when the decision-maker has sufficient information to estimate the expected outcomes associated with various alternatives. Uncertainty refers to future events when outcomes cannot be estimated from experience. Thus, one can make a rational response to risk on a probability basis, whereas response to uncertainty must be entirely subjective, and the reactions to it are characteristic of the individual. Currently, biologists are unable to make probability statements about the human medical consequences of routine feeding of antibiotics in livestock rations. They cannot predict that the treatment of a patient will be compromised in one in X number of cases. Therefore, we are confronted with uncertainty and not risk.

But even if the responsible decision-makers were provided with all the data that could be provided by exhaustive scientific investigation, their decision would still have to be a subjective judgment in which potential health benefits are balanced against economic benefits. Such a decision requires establishing priorities among societal goals. Conflicting goals must be balanced within a political society with differing priorities. Additional hearings could be held, but those who participate in hearings are not representative of every segment. Moreover, the views of certain groups, particularly the poor, are rarely well represented in legislative and administrative decision-making processes, while special-interest groups tend to be overrepresented.

Indirect Social Consequences

One of the important indirect effects of restricting the subtherapeutic or prophylactic use of antibiotics in animal feeds is the restriction it may place on the continued use of close confinement methods of animal production. Concentration of large numbers of animals under one manager in a small area was greatly facilitated by the discovery that incidence of disease could be reduced by routine feeding of antibiotics. The adoption of large-scale, highly capitalized operations has reduced the number of jobs in animal production and has irritated family farmers, rural communities, and urban areas which have received a large number of unskilled rural migrants (Marshall and Thompson, 1977; Rodefeld et al., 1978). Therefore, an important dimension of the issue is to determine the socioeconomic consequences of shifting back to more dispersed methods of animal production. Although large producers could reduce the risk of large-scale production by scattering the animals over a wider area, a shift toward more animal dispersal by larger producers would appear to improve the competitive position of smaller producers. Evidence from societies which have instituted land reform and the experience in areas in our own country in which large, nonfamily farms predominate would suggest the likelihood that increased use of less-intensive production methods could improve social conditions. Studies have shown that family farmers are much more involved in community activities and that communities located in areas characterized by family farms provide more services and a generally higher quality of life for their members than do communities in regions characterized by nonfamily farms (Goldschmidt, 1978; Heffernan, 1972; Heffernan and Lasley, 1978; Rodefeld, 1974).

Social Consequences Of Proposed Veterinary Prescriptions

The proposal to allow the use of antibiotic feed additives on a prescription basis raises issues that have serious implications for the organization of agriculture. This restriction has been in effect in England for some years, and there is no evidence that it has permanently influenced the amount of antibiotics used in livestock production. Feed-additive use of antibiotics without prescription seems to have been replaced by use on prescription (Braude, 1978). There is no reason to believe that the consequences would be different in the United States. Adoption of a regulation permitting feed-additive use of antibiotics on prescription only, however, could result in a higher level of social disorganization, stemming from less respect for government rules. The restriction would most likely be regarded as an obstacle for producers to work around, as the fees involved would represent an increased cost.

From the standpoint of the structure of agriculture, if any producers were unable to obtain a prescription for a feed additive, it would be the small producers. An advantage could thus accrue to large producers (such as cattle feedlots or integrated broiler-producing firms) because some larger producers employ their own staff veterinarian who could routinely write out the prescription. It would represent an advantage that larger producers would have over small producers, not as a result of increased efficiency, but as a result of having more readily available means for circumventing the regulation.

The veterinarian would not necessarily be engaging in an unethical procedure if he were to prescribe feed additives on a routine basis. The veterinarian's oath, as adopted by the American Veterinary Medical Association House of Delegates, July 1969, is:

> Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health, the relief of animal suffering, the conservation of livestock resources, the promotion of public health, and the advancement of medical knowledge. I will practice my profession conscientiously, with dignity, and in keeping with the principles of veterinary medical ethics. I accept as a lifelong obligation the continual improvement of my professional knowledge and competence.

The ethical charge to veterinarians is to serve society through the protection of animal health and not to make societal decisions. Because antibiotics are advantageous in maintaining good animal and human health under many conditions, the veterinarian would be doing that for which he is responsible if he were to prescribe the use of antibiotics. He would be benefiting society in certain ways, although not necessarily in all.

If the veterinarian were to adopt society's role in his professional decision-making, how would he decide? Even if he had the best information available, he would still have to make the decision that is impossible for society to make on an eminently objective basis. Some veterinarians would no doubt decide the issue in one way and others in another way.

To require a veterinarian's prescription for use of antibiotics in livestock and poultry production as a solution to the issue of human health risk that has been raised would be to transfer the decision-making from the government to a professional group that is certainly less representative of society than is the government. Adoption of such a course of action might be considered a sidestepping of responsibility by government, and certain political advantages might accrue. The issue, however, would remain. In fact, the issue would remain even if government were to accept the responsibility for deciding whether the risks exceed the benefits or vice versa. Another alternative would be to delay a decision, pending accumulation of more information about risks and benefits.

Economic Aspects of Drug and Chemical Feed Additives

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From: "Drugs in Livestock Feed," U.S. Congress, Office of Technology Assessment, June, 1979, Commissioned Paper

worked their way down through the chain of relationships in the economic system. Therefore, what happens to the impacted industry in the first two years following the ban on tetracyclines as feed additives may be quite different than the effects found four or five years hence.

For the reasons illustrated above, it is important to look at the impacted industries and consumers over a series of years to ascertain if the system tends toward equilibrium and, if so, what values the variables ultimately take. It is important to know if production of the products most directly impacted by forbidding the use of a feed additive technology will continue below levels that would have occurred without the regulatory action, or if production levels could be expected to recover. The movements of production of related products are also of interest over time. Price movements induced by a regulatory action such as forbidding the use of certain feed additives are also of interest in determining the impact on both the producer and the consumer.

Because of the importance of time considerations the analysis which will follow will include this dimension. The feed-livestock economy will be examined over a period of years following selected regulatory actions.

Empirical Analysis

At the present time, there are five scenarios that appear possible from the regulatory stance of the Food and Drug Administration. These are: (1) ban DES for beef cattle, (2) ban the sub-therapeutic use of tetracycline and penicillin preparations as feed additives, (3) ban the use of nitrofuran and sulfa compounds, (4) ban tetracycline and penicillin compounds along with nitrofurans and sulfa and (5) ban tetracyclines, penicillin, nitrofurans, sulfa and DES.

In this part of the paper these five scenarios will be examined for their economic impacts on consumers and producers. The analytical device used was a livestock-feed econometric model developed by the U. S. Department of Agriculture, Commodity Economics Division. With this model, it is possible to simulate a number of years of the livestock-feed economy to merely forecast future economic conditions or to examine the effects of perturbations in certain variables on other variables in the model.

The model used to analyze the impacts of the effects of the various feed additives combines the significant interrelations in the livestock-feed economy. There are 141 endogenous variables, values of which are determined by the model. In addition, there are 98 predetermined or exogenous variables measuring such elements as population, livestock and grain exports, various policy variables such as support prices and various other economic variables. The values of the exogenous variables, while determined outside the model, were not set at one level for the analysis, but were altered to reflect forecasts of economic conditions as well as could possibly be done.

The choice of a model for this analysis was constrained by the set of existing models. Two models were prominent. The chosen U.S.D.A. model developed by Teigen [13] and one by Paulsen, Mann, Rahn, Futrell and Ladd of Iowa State University [10] constituted the set available for this study. There are two major differences in the models. First, the U.S.D.A. model used an annual period of analysis, while the Iowa model used quarterly time periods. Second, feed prices were generated endogenously in the U.S.D.A. model, while they were exogenous in the Iowa model. Since analysis on a quarterly basis was not necessary for this analysis and since it is important for analyses covering extended periods of time

that fed prices be adjusted due to changes in demand for feed, the U.S.D.A. model was chosen.

Neither of these models were exactly suited for the purpose of this study since neither contain estimates of farm income or expenses. It is not possible to develop estimates of these values from the models since marketings are not estimated for all products. However, inferences about changes in farm income and expenses due to the introduction or removal of feed additives can be drawn from the behavior of prices of meat animals and feed.

To assess the effect of various feed additives on the livestock-feed economy, the model was perturbed by shifting the relevant supply curve(s) similar to the effect shown in Figures 1, 2 and 3. By running the model through a number of periods after the supply curve shift, the behavior of production, prices, consumption, etc. was modeled.

It is important to note the differences between the analysis proposed here and that done in previous studies of the economic aspects of feed additives. Studies on antibiotics by Henry Gilliam and J. Rod Martin [5] for beef and pork and by George Allen and Clark Burbee [1] on broilers and turkeys used the technique of comparative static analysis and compared the economic equilibrium of the system before and after banning a feed additive. A similar technique was used in a U.S.D.A. study on DES [16]. In so doing these studies tended to generate one number as the annual cost or gain to consumers or producers using an aggregation based on animal numbers. In reality, every year in the future will be different as farmers, ranchers, and consumers, and foreign countries all adjust to the new information that each year brings. So there is no one measure of impact on farm income for example, but rather a trend relative to what farm income might have been without the technological effect resulting from regulation. A study by Thomas Mann

and Arnold Paulsen [8] used the Iowa State econometric model to simulate the effects of banning what they characterized as "all antibiotics" and DES. However, their model was the Iowa State quarterly model which probably provides more detail on prices and production than needed for this study. In addition, the model used by Paulsen and Mann treated feed prices as exogenous variables, a situation not desirable for any long-term simulations where feed prices are the result of a demand for feed derived from animal feeding. Nevertheless, Paulsen and Mann effectively demonstrated the usefulness of the simulation approach in analyzing the kinds of effects represented by the introduction or removal of a feed additive drug or chemical as well as the influence of substitutes.

Scenario I: Ban DES

Due to concern over carcinogenicity, the use of DES in cattle feed was banned by the FDA in January of 1973. The use of DES as an implant was banned in April 1973. Since that time legal questions have been raised concerning the banning and the use has been reinstated pending the outcome of court proceedings. The future of DES is still uncertain.

There are three previous studies that were reviewed dealing with the economic aspects of DES. The study by Mann and Paulsen mentioned earlier [8], a study by the U.S.D.A. in 1971 presented at congressional hearings [16] and a Ph.D. thesis at the University of Missouri (Columbia) by Mohammed Sulieman [12]. All of these studies have been done since 1970. The Sulieman and the U.S.D.A. studies both used comparative static analyses and estimated shifts in the supply curves equivalent to a 2.7% to 3.75% reduction in beef supply respectively, assuming that the same number of animals are fed for the same feeding periods. Mann and Paulsen [8] used an econometric model to simulate the effects of the DES ban on the industry and found the impact to be minimal. Part of the difference

for beef could amount to as much as $12 per capita in the initial years to a benefit of about $3 per capita in years 5 and 6 where simulated prices were low. The average per capita cost would be at about the $5.70 level. Increased annual per capita expenditures for pork would be about $1.30, for broilers about $0.55 and for turkey about $0.20. The net result will be increased costs of about $5.70 + $1.30 + $0.55 + $0.20 = $7.75 per capita, or about $1.7 billion increase in consumer expenditures for meat.

There are substitute materials for DES however. One material called Synovex can be used as a substitute for DES on steers and melengestrol acetate which suppresses estrus in heifers can be used to provide the growth promotion and feed efficiency effects attributed to DES. If these are as effective as DES then the ban would be minimal. If they are only partially as effective as DES then the impacts would be a fraction of those presented here. If, conservatively, Synovex and melengestrol acetate are only half as effective as DES, the price and consumption effects shown in Figures 4 and 5 and Tables 1, 2 and 3 could be halved to present a fair picture of the impacts.

Scenario II: Banning Tetracyclines and Penicillin.

Sub-therapeutic dosages of tetracyclines and penicillin are used throughout the meat producing industry to (1) provide growth promotion and feed efficiency, (2) protect against infectious diseases such as bacterial scours, respiratory diseases, etc., (3) provide for control of disease where it already exists. The principal uses for meat animals are for pork and poultry. Tetracycline compounds are used in fed beef production to prevent liver abscesses that result in condemned livers and a minor loss of revenue. Tetracycline compounds are also used in fed beef production to prevent shipping fever.

Earlier studies by Dworkin [3] for cattle and swine and Allen and Burbee [1] for poultry provide previous summaries of the effects of antibiotics on meat producing animals. In addition, the studies by Gilliam and Martin [5] and Mann and Paulsen [8] provide insight into effects of tetracyclines and penicillin.

The supply shifts for beef and pork were adopted from the Dworkin work for the simulation on this scenario and the supply shifts for chickens and turkeys were adopted from the Allen and Burbee study. Substitutes were not considered in this simulation and no allowance was made for changes in mortality which knowledgeable readers will recognize as data extremely difficult to obtain.

The key elements in the Dworkin analysis are:

1. Fed cattle comprise 75% of total commercial slaughter.
2. Antibiotic fed cattle comprise 60% of commercial slaughter. (Thus, 80% of fed cattle receive sub-therapeutic antibiotics.)
3. All pigs and hogs are fed. All fed pigs and 85% of fed hogs receive antibiotics in feed.
4. The absence of tetracyclines would result in a 25.6% increase in liver abscesses in feedlot cattle and a 5% increase in cervical abscesses in hogs [3, p. iv].

The key elements of the Allen and Burbee analysis are:

1. All broilers and turkeys are fed antibiotics.
2. Antibiotic feeding improves broiler gain per day by 2.2%.
3. Antibiotic feeding reduces feed per pound of gain for broilers by 2%.
4. Mortality for chick replacements is 3%.
5. Antibiotic feeding improves turkey rate of gain per day by 3.2% for hens and by 3.2% for toms.
6. Antibiotic feeding reduces feed per pound of gain for turkeys by 5% for hens and by 8% for toms.
7. The average mortality is 9% for poult replacements [1, p. 18, 35].

Shifts in the supply curves of all four major meats to represent increases in the unit costs of production were as follows: (1) beef, -1%, (2) pork, -4%, (3) broilers, -2.2%, and (4) turkeys, -3.2%. These amounted to quantity impacts of (1) beef, 260 million lbs., (2) pork, 497 million lbs., (3) broilers, 199 million lbs., and (4) turkeys, 66 million lbs.

Results from the simulation were much like the DES scenario except that the levels of effects on the products were different. Changes in civilian consumption are shown in Figure 6 and changes in the prices of meat animals are shown in Figure 7. Tables 4, 5 and 6 show percentage change in consumption, animal prices and retail price indices respectively.

Banning of the sub-therapeutic uses of tetracyclines and penicillin has the effect of lowering by a little more than 2 pounds per capita the civilian consumption of pork. The farm price of pork increased by. 4.5 to 7.1 percent, while consumption was reduced by about 3 percent. indicating increased incomes for producers. Beef consumption was reduced relatively little, while fed and non-fed cattle prices either showed no change in two years or increased by up to about 3 percent. So, beef producers were affected less dramatically than pork or poultry producers.

Young chicken consumption could be expected to be reduced slightly on the average with prices significantly higher due to the impact of the banning on the pork supply. In the case of turkey, the consumption was reduced more percentagewise and the price could be expected to increase relatively more.

The importance of the cross elasticity of demand is seen in this scenario again as pork and poultry prices tend to move together, with beef prices rather more independent in movement. There would no doubt be an increase in abscessed beef livers estimated to be a total of

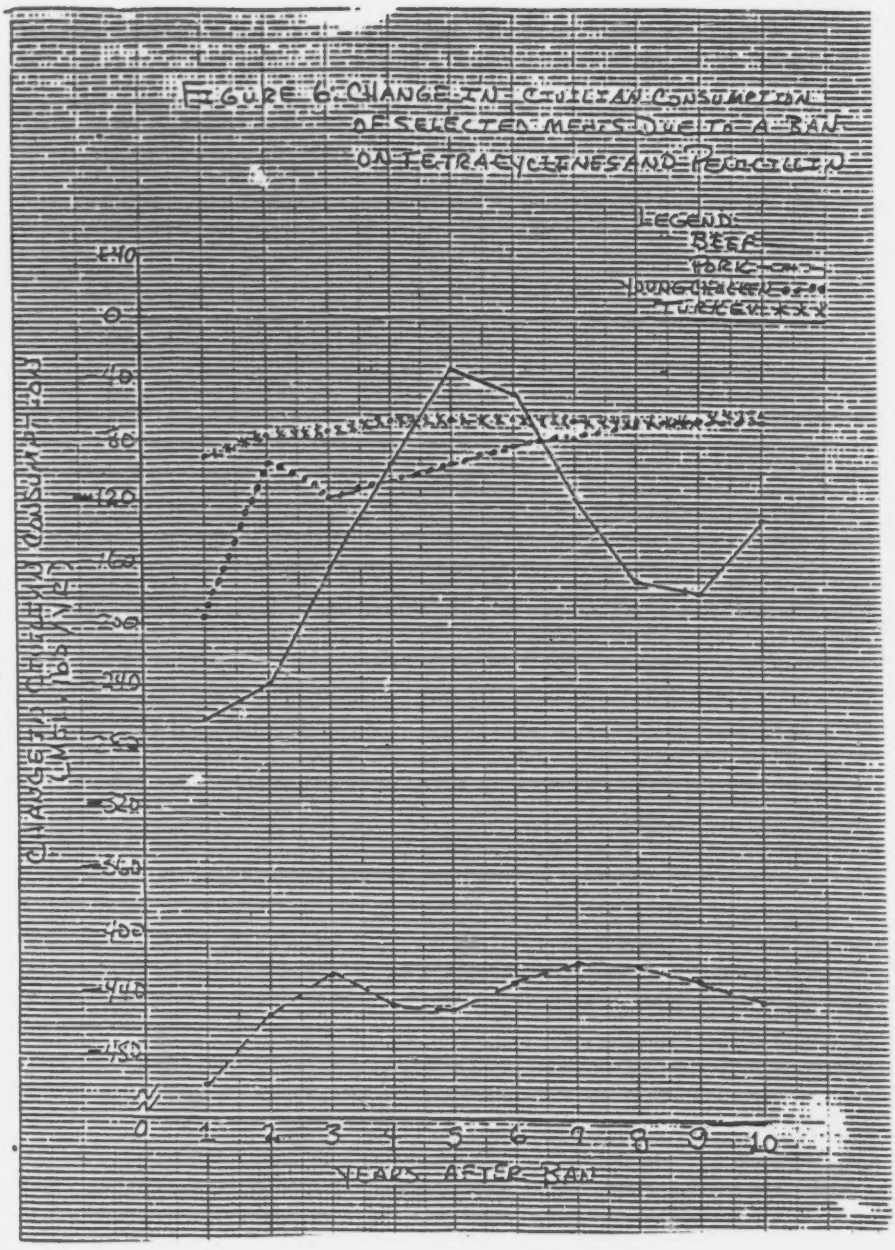
FIGURE 6. CHANGE IN CIVILIAN CONSUMPTION OF SELECTED MEATS DUE TO A BAN ON TETRACYCLINES AND PENICILLIN
LEGEND:
BEEF
PORK
CHICKEN
TURKEY
+40
0
-40
-80
-120
-160
-200
-240
-280
-320
-360
-400
-440
-480
-520
0
1
2
3
4
5
6
7
8
9
10
YEARS AFTER BAN

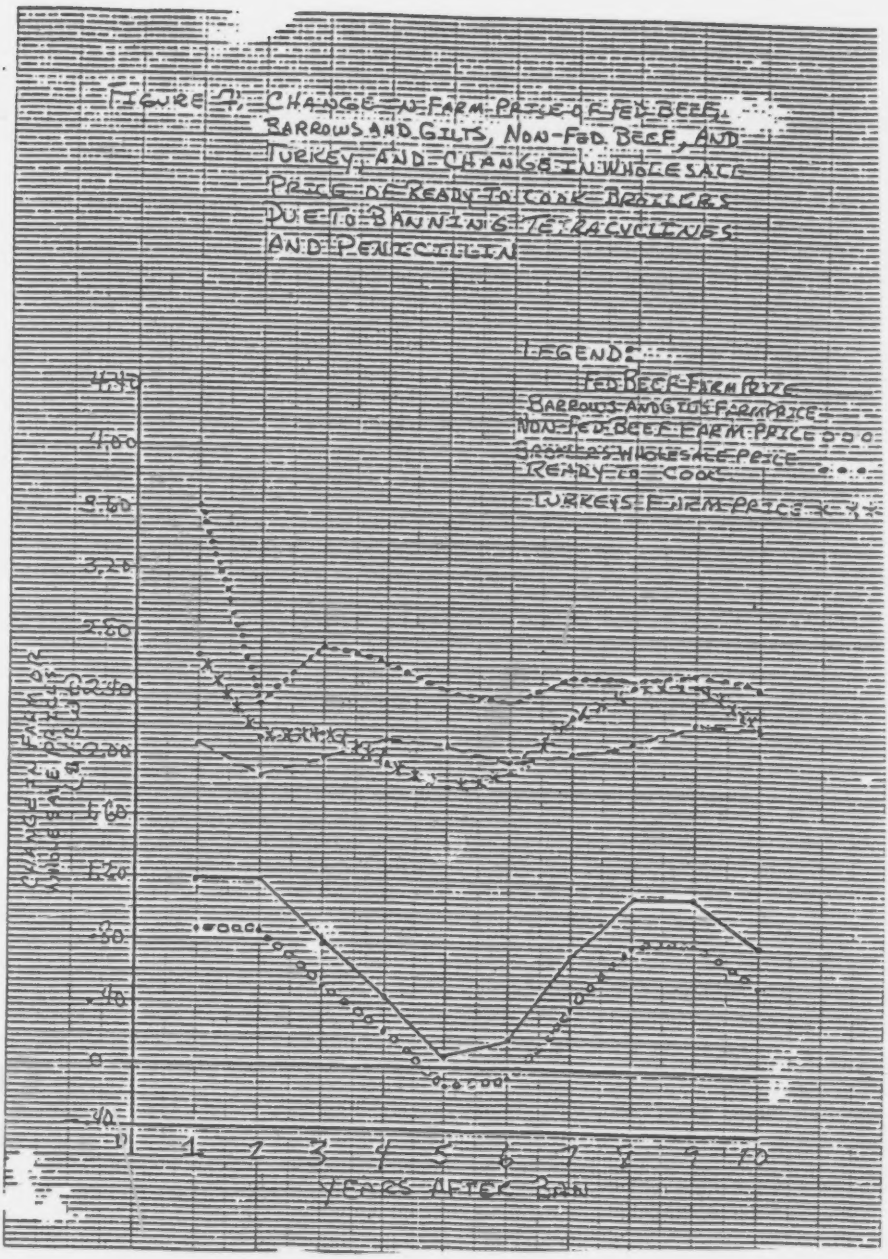
FIGURE 4.—CHANGE IN FARM PRICE OF FED BEEF, BARROWS AND GILTS, NON-FED BEEF, AND TURKEY, AND CHANGE IN WHOLESALE PRICE OF READY-TO-COOK BROILERS DUE TO BANNING TETRACYCLINES AND PENICILLIN
LEGEND:
FED BEEF FARM PRICE
BARROWS AND GILTS FARM PRICE
NON-FED BEEF FARM PRICE
BROILERS WHOLESALE PRICE READY TO COOK
TURKEYS FARM PRICE
4.80
4.40
4.00
3.60
3.20
2.80
2.40
2.00
1.60
1.20
.80
.40
0
-.40
1 2 3 4 5 6 7 8 9 10
YEARS AFTER BAN

Table 4: Percent Change in Annual Civilian Consumption of Selected Meat Products Due to Banning Tetracyclines and Penicillin.

Year	Beef	Pork	Young Chicken	Turkey
1	-1.0	-3.6	-2.4	-4.8
2	-1.0	-3.4	-1.1	-4.2
3	-0.6	-3.5	-1.3	-3.7
4	-0.3	-3.4	-1.2	-3.3
5	-0.1	-3.3	-1.0	-3.3
6	-0.2	-3.0	-0.9	-3.1
7	-0.4	-2.8	-0.8	-3.1
8	-0.6	-2.8	-0.7	-3.0
9	-0.6	-2.9	-0.7	-2.9
10	-0.4	-3.0	-0.7	-2.7

Table 5: Percent Change in Farm Price Liveweight for Fed Cattle, Non-Fed Cattle, Turkeys, Barrows and Gilts, and Wholesale Price of Broilers Ready to Cook, Due to Banning Tetracyclines and Penicillin.

Year	Fed Cattle Farm Price	Non-Fed Cattle Farm Price	Barrows and Gilts Farm Price	Turkey Farm Price	Broilers Whsl. Price
1	+3.1	+3.6	+7.1	+ 9.5	+10.9
2	+2.4	+2.9	+4.9	+ 5.8	+ 5.9
3	+2.0	+2.1	+4.5	+ 7.5	+ 7.7
4	+1.1	+0.9	+4.8	+ 7.1	+ 6.1
5	+0.1	-0.4	+5.1	+ 6.3	+ 6.5
6	+0.4	-0.3	+5.2	+ 8.7	+ 6.9
7	+1.5	+1.2	+5.3	+ 9.8	+ 7.0
8	+2.4	+2.4	+5.6	+12.1	+ 7.5
9	+2.8	+3.0	+6.1	+15.5	+ 7.8
10	+2.1	+2.2	+6.0	+14.0	+ 7.6

Table 6: Percent Change in Retail Price, 1967=100 Indices for Beef, Pork and Meat,* Due to Banning Tetracyclines and Penicillin.

Year	Beef	Pork	Meat
1	+2.5	+6.5	+4.7
2	+1.9	+4.8	+3.3
3	+1.6	+4.6	+3.4
4	+0.9	+4.7	+3.0
5	+0.2	+5.0	+2.6
6	+0.4	+5.3	+2.8
7	+1.2	+5.4	+3.3
8	+1.9	+5.7	+3.8
9	+2.2	+5.9	+4.2
10	+1.7	+5.9	+3.9

*Meat Includes Beef, Pork, Chicken and Turkey

40 percent of the livers of fed beef. Based on a fed beef slaughter of about 30 million head, this would be 12 million livers with a wholesale value of from $35 to $40 million. This would represent an increase of about $20 million per year due to liver abscesses.

The $2.00 per cwt. increase in pork prices would result in about 3.9 cents per pound at retail. With consumption in the 65 pound per capita range, this amounts to about $2.50 per capita increase in expenditures for pork. The increase in the chicken price of about $2.50 per cwt., ignoring the initial impact would mean an increase in retail prices of about 3.5 cents per pound. With per capita consumption in the 40 pound range this is a $1.40 per capita increase in expenditures for young chicken. The turkey impact would be minimal since the consumption is so small per capita. Beef retail price impact would be about 1.5 cents per pound or $1.80 per capita. So the total impact per capita would be about $1.80 + $1.40 + $2.50 = $5.70 per capita or about $1.2 billion total increase in consumer expenditures for meat.

There are substitutes for the tetracyclines and penicillin for swine, chickens and turkeys. Two of the most often mentioned are tylosin and bacitracin. Allen and Burbee concluded after examining data on the effects of antibiotics on poultry that tylosin and bacitracin are excellent substitutes for the tetracyclines and penicillin [1, p. 15]. Therefore, with these materials as well as others such as erythromycin and the arsenicals, there would likely be a minimal impact on poultry from banning tetracyclines and penicillin.

In the case of pork and beef, tylosin and bacitracin are viable substitutes for the tetracyclines and penicillin. Dworkin concluded that zinc bacitracin will give equivalent growth promotion in cattle, while allowing an increased incidence of shipping fever and liver abscesses.

Dworkin further concluded that tylosin in swine gives equal control of atrophic rhinitis when combined with sulfa and equal growth promotion for feeder pigs. For slaughter hogs, tylosin alone gives equal growth promotion, but may not control cervical abscesses [3, p. 6]. The presence of these substitutes could mitigate the impact considerably. Certainly the $20 million increase in liver abscess losses would remain, but perhaps the other impacts would be small with consumers ultimately paying for the condemned livers and any increases in costs of the substitute medications.

Scenario III: Banning Nitrofurans and Sulfa.

Nitrofuran compounds are used to control a number of bacterial diseases in swine, chickens and turkeys as well as for growth promotion and feed efficiency. In addition, nitrofuran compounds such as furazolidone aid in the control of coccidiosis in chickens and turkeys. Nitrofurans have no uses in beef production.

The sulfa drugs have uses in chicken and turkey production to control fowl chloera and coccidiosis. Sulfa is sometimes combined with chlortetracycline and administered to swine to reduce cervical abscesses. In beef production, chlortetracycline and sulfamethazine are used in combination to control respiratory diseases such as shipping fever.

In analyzing this scenario where both groups of drugs are banned, the supply shifts were applied to pork, broilers and turkeys only. Initial supply shifts of -2.5% for pork, -12% for broilers, -12% for turkeys were assumed. These amount to 310 million lbs. for pork, 1078 million lbs. for chicken and 247 million lbs. for turkey. These estimates were based on the inflation impact statement for nitrofurans prepared by F.D.A. in May 1976 [17]. This statement was based on a range of from 0-5% negative supply impact on pork and 2-20% negative supply impact on poultry from banning nitrofurans alone, but still having sulfa available. The report went on to say

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Released 9/18/77

REPORT OF THE COMPTROLLER GENERAL OF THE UNITED STATES

Need To Establish Safety And Effectiveness Of Antibiotics Used In Animal Feeds

Food and Drug Administration
Department of
Health, Education, and Welfare

Antibiotics are used at low levels in the feed of most food-producing animals to promote growth and prevent disease. Because many of these antibiotics are also used to treat disease in humans or animals, the development of antibiotic-resistant bacteria due to the use of antibiotics in animal feeds may lessen the effectiveness of antibiotics in treating human and animal diseases.

The Food and Drug Administration has permitted the continued use of low levels of a number of antibiotics in animal feed even though the safety and effectiveness of such use has not been established. On April 15, 1977, the agency's Commissioner announced the decision to restrict the use of penicillin, tetracyclines, and sulfaquinoxaline used in animal feeds.

HRD-77-81

JUNE 27, 1977

demonstrate the safety and effectiveness of new animal drugs. FDA's Bureau of Foods assists BVM by reviewing data submitted to demonstrate the safety of any drug-related residues in food. 1/

HOW ARE ANTIBIOTICS USED IN ANIMAL FEEDS?

Antibiotics are chemical substances produced wholly or partially by a microorganism which has the capacity to inhibit the growth of, or to destroy, bacteria and other microorganisms. In addition to the true antibiotics such as penicillin and the tetracyclines, other antibacterials such as the sulfonamides and nitrofurans, have been developed. For the purposes of this report, the term "antibiotics" will refer to true antibiotics and the sulfonamides and nitrofurans.

Antibiotics are used in veterinary medicine not only at therapeutic levels to treat animal diseases, but also at subtherapeutic levels to prevent disease, promote growth, and increase feed efficiency (i.e., increase the amount of weight gained per pound of feed consumed). Subtherapeutic levels of antibiotics are administered to food-producing animals, including swine, poultry, and beef cattle, through the use of medicated feeds.

The ability of antibiotics to increase the growth rate of animals (often accompanied by a decrease in the total feed consumption) was discovered in the early 1950s. Since then, the practice of adding antibiotics to animal feed has steadily increased. Between 1960 and 1970 the use of antibiotics in animal feeds increased approximately sixfold. In 1970 antibiotics used in animal feeds represented about 43 percent of the approximately 17 million pounds used for all purposes.

It was estimated that virtually 100 percent of the chickens and turkeys, about 90 percent of the swine and veal calves, and about 60 percent of the cattle raised in the United States during 1970 received antibiotics in their feed.

1/Up until Jan. 1, 1966, when BVM was established, the Bureau of Medicine was responsible for regulating both human and animal drugs.

The Bureaus of Foods and Drugs were established on Feb. 1, 1970. Before then, the functions of the Bureaus of Foods and Drugs were divided among the former Bureaus of Medicine, Science, and Compliance.

The amount of antibiotic included in animal feeds depends upon its intended function. Up to 50 grams of an antibiotic are added per ton of feed to promote growth and/or increase feed efficiency and 50 to 200 grams are added per ton of feed to prevent disease. Concentrations of antibiotics exceeding 200 grams per ton are considered therapeutic dosages.

Antibiotics used in animal feeds include procaine penicillin, tetracyclines (oxytetracycline and chlortetracycline), tylosin, bacitracin, neomycin sulfate, streptomycin, erythromycin, sulfamethazine, oleandomycin, novobiocin, lincomycin, virginiamycin, furazolidone, nitrofurazone, sulfadimethoxine, sulfaquinoxaline, monensin, sulfathiazole, and flavomycin.

Many of these antibiotics are also used in human therapy.

WHAT IS ANTIBIOTIC RESISTANCE?

A bacterial strain is considered resistant when a genetic change allows it to tolerate a significant increase of an antibiotic concentration. Bacteria may become antibiotic resistant by spontaneous chromosomal mutation (an inheritable change of an individual gene which may alter its functions) or by transfer of a small independent genetic element known as a resistance factor, or R-factor (also known as a resistance plasmid), from a resistant microorganism to a sensitive one. Two other kinds of resistance are phage mediated 1/ and inductive 2/.

A strain of an organism which has developed resistance to one antibiotic may exhibit resistance to other antibiotics to which it has not been exposed, especially if the antibiotics are chemically similar or act in similar ways. In addition, some resistant organisms may transfer antibiotic resistance to other organisms through contact with them. This phenomenon is known as transferable drug resistance.

Although only one or two organisms in a large population of bacteria may initially exhibit a degree of antibiotic resistance, a large population of resistant organisms may quickly develop in the presence of the antibiotic.

1/A phage, or bacteriophage, is a virus of a bacterium that may transfer bacterial resistance.

2/In inductive resistance the antibiotic directly influences the bacterial cell to produce a new chemical within the bacterium that now renders it resistant to the antibiotic.

APPENDIX II

STATEMENT OF THE ANIMAL HEALTH INSTITUTE
ON THE USE OF ANTIBIOTICS IN ANIMAL FEED
Before the
SUBCOMMITTEE ON INVESTIGATIONS & OVERSIGHT
HOUSE COMMITTEE ON SCIENCE & TECHNOLOGY

Tuesday, December 18, 1984

The Animal Health Institute (AHI) is the national trade association representing U.S. manufacturers of animal health and nutrition products. Its members are involved in the discovery, development, and marketing of feed additives, including antibiotics that meet the needs of animal producers and thus ultimately benefit the American consumer. AHI and its members have participated directly in the decades of review of the safe and effective use of antibiotics in animal agriculture.

The interest of AHI is not in any particular drug. Rather, it is in the process by which drugs are approved or later withdrawn from the market under the provisions of the Federal Food, Drug, and Cosmetic Act. That Act mandates the rigorous application of scientific standards to any application for the marketing of a new animal drug. The new animal drug provisions of the Act, added in 1968, but representing a coalescence of standards dating back to 1938, require the submission by an applicant of "adequate tests by all methods reasonably applicable to show whether or not the drug is safe. . .." In addition, the applicant must supply "substantial evidence" that the drug is effective. Given the importance of animal drugs, both to the agricultural

community and to all U.S. citizens who consume the resulting meat, milk and eggs, FDA justifiably requires a rigorous evaluation of the data submitted in support of animal drug applications.

Once an application is approved, there has been a considerable expenditure of research funds, and considerable additional time and effort to bring a drug to market. Such investments, and the benefits they bring to the farmer and to the consumer, should not be overturned lightly. Rather, we believe that the "new evidence" test in the Act for initiating withdrawal proceedings imposes the same rigor of scientific inquiry as is required in the approval process. The court decisions interpreting the withdrawal provisions of the Act support our view that there is a clearcut burden on those seeking to have drugs withdrawn from the market to demonstrate that their new evidence is not speculative, but meets the same high scientific standards as are applicable to the approval process.

AHI is dismayed with the use of speculation, misstatement, and indeed, fear in lieu of rational scientific analysis by those seeking the ban of certain feed use antibiotics. It is AHI's position that the studies upon which these persons rely, when subjected to a rigorous scientific analysis, fall far short of providing the kind of rational scientific support that either sound public policy or the

Food and Drug Act requires in support of a proposal to remove any drug from the market.

The study most widely pointed to is that by Dr. Holmberg and others, entitled "Drug Resistant Salmonella From Animals Fed Antimicrobials" in the September 6, 1984 New England Journal of Medicine. Despite the assertion by Dr. Stewart Levy in the same issue of the New England Journal that this study provides a "important missing link", a careful evaluation of the study demonstrates that it fails to provide sound scientific evidence that the subtherapeutic use of antibiotics engenders antibiotic resistant disease in humans.

It is unfortunate that so much of the study rests upon speculation and assumption. It is also unfortunate that the study centered so strongly on salmonella, which is one of the few pathogens common to animals and humans. As a commentator recently observed,

> "[I]t is fascile to point to this case as proof that subtherapeutic antibiotics in animals can lead to antibiotic-resistant diseases in humans . . .. Just as it has been insufficient merely to lay out the theoretical possibility that resistance in animal bacteria could be transferred to human pathogens (a possibility that no one disputes), so it is insufficient to demonstrate, however elegantly, that meat contaminated with resistant salmonella can make people ill."

The study by Dr. Holmberg and his colleagues involved 18 patients from four Midwestern states who had contracted infection of a specific Salmonella Newport serotype. These

patients had food poisoning while they were simultaneously on oral antibiotics (often self-prescribed). Holmberg claims to have linked that outbreak of salmonellosis to the subtherapeutic use of chlortetracycline in cattle feed. It is unfortunate that an article that contains some quite elegant scientific investigations lapses in these conclusions to rank speculation and assumption.

No evidence is presented in the study that the Salmonella Newport serotype was ever present in the South Dakota beef farm alleged to be the source of the contaminated meat. The authors do not even indicate whether they attempted to isolate salmonella from humans, animals, or meat products from that beef farm. Certainly, they never could show this serotype in either the animals that were reduced to hamburger or in the hamburger itself that supposedly was eaten by the 18 patients, for all those animals had long since been slaughtered and the meat consumed.

The closest that Holmberg and his colleagues come is in pointing to this particular Salmonella Newport plasmid profile as having been cultured from the tissues of one dead calf from a dairy herd adjacent to the beef farm in question. That dairy farm had suffered an outbreak of diarrhea, but there is no report with respect to the antibiotic usage on the dairy farm, which is the only place where this particular "fingerprint" was found. While Holmberg suggests that there was some interaction between the animals on the dairy farm and the beef farm, it is probably worse than speculation to suggest that a dairy calf with diarrhea

was more likely to have obtained the resistant plasmid from the beef farm than to have transmitted the resistant plasmid to the beef farm.

In any event, that fingerprint never appears on the beef farm. It thus becomes total speculation and assumption that somehow that beef herd contained the fingerprint, and that that fingerprint traced through the slaughter, production of the ground meat, and distribution of the ground meat to supermarkets where it was eaten by the 18 patients. What starts out quite scientifically, in identifying the plasmid "fingerprint" in the human illness and in this one diseased calf, breaks down into speculation with respect to a totally different set of animals on an entirely different location, where there is no evidence of the presence of the "fingerprint."

While Dr. Holmberg's speculation may easily fit into his preconceived notions of the hazards of the use of antibiotics and the transmission of resistant organisms from animals to man, it is unfortunate that he took no steps to try to document his assumptions or prove his speculation.

Dr. Holmberg's speculations are perhaps rendered less credible when one considers two other facts. First, the meat from the beef farm in question was mixed with meat from many other sources, and widely distributed. However, there is no report of similarly widespread occurrence of food poisoning despite the fact that individuals undoubtedly have undergone antibiotic

therapy in areas outside of the Minneapolis area where they would have been as likely to have consumed meat from this widespread distribution.

Second, the report itself belies the suggestion that there should be implicated the subtherapeutic use of antibiotics in animal agriculture. The author's report of a hundred grams of chlortetracycline per ton of feed would indicate more than a gram of chlortetracycline per animal per day. This is a level above subtherapeutic levels but within the therapeutic range. It thus contradicts the author's statement that the beef cattle in question received "no therapeutic concentrations of antimicrobials."

A second article by Holmberg and others, "Animal-to-Man Transmission of Antimicrobial-Resistant Salmonella: Investigations of U.S. Outbreaks, 1971-1983", appearing in the August 24, 1984 edition of Science, similarly is unable to withstand careful and critical scrutiny. In this paper, Holmberg and his co-authors examine the origin and severity of some 52 reported salmonella outbreaks over the 12-year period, stating that the 20-to-30 percent of salmonella isolates are now antibiotic resistance, and inferring that this represents a significant increase. In fact, earlier surveys done by Ryder and others in 1967 and 1975, also show that some 20-31 percent of all salmonella serotypes were resistant to one or more antibiotic. These data in fact do not suggest a change in the proportion of antibiotic resistance among all salmonella serotypes over the past two decades.

This Holmberg report also raises the need to study the difference between "correlation" and "causal relationship." Antimicrobial therapy is normally contraindicated in enteric salmonella infections, most of which are mild and self-limiting. Patients suffering from systemic infection and high risk patients such as infants and the elderly, would be much more likely to receive antimicrobial therapy. Therapy in this kind of systemic infection may result in selection for resistant organisms in patients involved, and isolations from such patients would normally be expected to yield a high incidence of resistant organisms. Higher mortality would also be expected in these classes of high risk patients. Therefore, while these two phenomena might well occur in the same group, it would be wrong to imply a causal relationship from resistant organisms. It is just as difficult to ascertain the antibiotic sensitivity of the infecting organisms prior to treatment and hence the validity of the author's classification scheme.

Two other studies perhaps bear mentioning, as they represent quite elegant work, but not work that bears any direct relationship to the issue of the role of low level antibiotics in the creation of antibacterial resistance that might be transmittable to man.

For example, the study by Dr. O'Brian and his colleagues, also reported in the New England Journal of Medicine, presents a highly sophisticated and new scientific technique for the typing and classification of salmonella plasmids. This elegant new

approach will eventually be of great use in epidemiology, but the findings of this work can not be used to implicate the use of low level antibiotics in human health, because there was no study of particular sourcing of the materials being studied.

Similarly, the recently released final report of the study "Surveillance and Flow of Salmonella and Campylobacteria in a Community" raises significant issues concerning the proper handling of meat in the food supply chain, but it does not, nor is it designed, to provide information with respect to the effect of the use of antibiotics on farms and the development and transmission of antibacterial resistance. As the authors themselves point out:

> "When chicken isolates were divided into those associated with processor and retailer products, there was a greater prevalance of resistance among retail products to four of the five antibiotics tested...."

FDA has, in this study, contracted an elegant piece of research on the natural history of campylobacteriosis and has identified several sources of this important enteric pathogen. However, from the standpoint of elucidating the role of feed antibiotics in the prevalence of antibiotic resistance patterns of these organisms, the report provides only speculation and not evidence.

AHI would like to return to the main point of its presentation: Manufacturers are entitled to the same rigorous and carefully-evaluated scientific studies when charges are levied against products as are required of manufacturers in order to get

products on to the market. Speculation, supposition, and leaps of logic or faith are not the basis upon which years of investment, and significant and important use by the animal health community should be wiped out. The studies most recently cited as demonstrating the existence of a significant public health issue can not stand up to a rigorous evaluation. Rather, they have significant data gaps, and quite explicit assumptions rather than scientific evalutions or determinations. AHI strongly urges the use of the best science, and objects to the use of speculative or sensational techniques in lieu of good science in challenging the continued marketing of animal antibiotics.

PUBLIC VOICE FOR FOOD & HEALTH POLICY

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Statement of
Public Voice for Food and Health Policy
In Connection with the December 18-19, 1984, Hearings
Before the
Subcommittee on Investigations and Oversight
Committee on Science and Technology
U.S. House of Representatives

Public Voice for Food and Health Policy appreciates the opportunity to comment on the troubling problems surrounding the subtherapeutic use of antibiotics in animal feed. Public Voice is a non-profit consumer research and advocacy organization working on food, nutrition and agricultural issues. We seek to ensure that every American has access to safe, nutritious and affordable food. In pursuit of these goals, Public Voice has joined with a broad coalition of scientists, environmental groups, consumer advocates, and others in calling for an immediate ban on the subtherapeutic use of penicillin and tetracyclines in animal feed.

In our comments today, we wish to emphasize two points: first, that restricting the use of antibiotics in animal feed is a matter of basic food safety; and second, that in light of current scientific knowledge, it is time for regulatory action--not further study.

A Matter of Basic Food Safety

Meat, of course, plays a central role in the nutritional life of our nation. As the National Cattlemen's Association pointed out in its prepared statement at the Subcommittee's December 18, 1984, hearing, "the supply of wholesome and nutritious animal products, available to the consumer in this country, has contributed immeasurably to the excellent health of Americans." Accordingly, it is essential that Americans be assured that the meat they eat is safe.

Since the 1950s and early 1960s, when the practice of feeding antibiotics to livestock became widespread, scientists have feared that this practice might result in meat becoming a transmitter of antibiotic-resistant diseases. Recently completed studies show that these fears were well founded. In particular, the studies demonstrate that the practice of feeding subtherapeutic doses of antibiotics to animals creates a strong evolutionary pressure for the development of antibiotic-resistant bacteria in animals, and that these resistant animal bacteria can infect people who eat meat or have other forms of contact with livestock. As a result, people may become sick with diseases which cannot be treated by the usual (and safest) medicines.

This disturbing chain of events was illustrated most dramatically in the recent report by Dr. Scott Holmberg and his colleagues at the Centers for Disease Control (CDC).[1] Confronted with an

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[1]Holmberg et al., Drug-Resistant Salmonella from Animals Fed Antimicrobials, 311 New Eng. J. Med. 617 (Sept. 6, 1984).

outbreak of 18 cases of Salmonella newport in four midwestern states, the CDC team painstakingly traced the source of the infection to a single beef herd in South Dakota. The CDC researchers concluded that the herd, which had been fed subtherapeutic doses of chlortetracycline, had developed an antibiotic-resistant strain of Salmonella. Meat from the herd was distributed to stores in several states, and when consumers ate the meat, they ingested the antibiotic-resistant bacteria. Some of these people, particularly those who had been taking antibiotics for other reasons (thereby removing ecological competition for the new bacteria), became sick with severe Salmonella infections. Many had to be hospitalized, and, tragically, one died. The CDC study, thus, serves as a sobering reminder that the dangers posed by the use of antibiotics in animal feed are not merely theoretical, but all too real.

Another such reminder was provided a few months ago by an exhaustive study performed by the Seattle-King County Department of Public Health under contract from the Food and Drug Administration.[2] Unlike the CDC study, the Seattle study dealt with antibiotic resistance in poultry. It showed, among other results: (1) that almost one-fourth of retail poultry was contaminated with either Salmonella or Campylobacter infections, (2) that people contracted these infections by eating the contaminated poultry, (3) that there was a high rate of bacterial resistance

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2 "Surveillance of the Flow of Salmonella and Campylobacter in a Community, U.S. Contract No. 223-81-7041 (August 1984).

to tetracyclines and other antibiotics in both people and poultry (with respect to tetracyclines, 29.8% and 32.8% respectively[3]), and (4) that the bacteria were able to transfer the resistance trait to other bacteria by means of plasmid carriage.

These findings plainly indicate that the Salmonella outbreak described in the CDC study was not an isolated case and that contamination of meat with antibiotic-resistant bacteria has become a serious problem. As a consumer advocates, we at Public Voice strongly believe that the public ought to be protected from such food safety hazards.

A Time for Action

We anticipate that opponents of the proposed ban on the subtherapeutic use of penicillin and tetracyclines in animal feed may acknowledge the gravity of the food safety risks involved, but plead that more research is needed before any restrictions are imposed. We reject that argument. In our view, the necessary scientific prerequisites for a ban are already firmly in place.

First, there is little dispute that antibiotic resistance has become an increasingly prominent human health problem. Second, it has long been clear that antibiotic use in either animals or humans creates biological incentives for the development of antibiotic-resistant bacteria. Moreover, since animal feed accounts for roughly half the antibiotics used in this country, it obviously plays a significant role in creating such incentives.

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[3] Id. at 169.

Opponents of the ban have sought to minimize the importance of these facts by arguing that bacteria in humans do not mingle with bacteria in animals, and that, accordingly, resistance to antibiotics cannot be transferred from animals to people. Whatever persuasiveness this argument may have once had, it has now been clearly demonstrated to be false, not only by the CDC and Seattle studies already mentioned, but also by the study published in 1982 by Dr. Thomas O'Brien and his associates at the Harvard Medical School.[4]

Using new techniques, Dr. O'Brien was able to show that plasmids found in humans were virtually identical to those found in animals. Such close similarities, he concluded, demonstrated that plasmids, such as those that carry the antibiotic-resistance trait, pass freely between animals and humans.

In light of this fundamental finding, it is not at all surprising that in October 1983, prior to the publication of the CDC and Seattle studies, 300 leading scientists from across the country signed a joint statement calling on the federal government to act quickly to ban subtherapeutic uses of penicillin and tetracyclines in animal feeds. Now, with the additional support provided by the CDC and Seattle studies, the scientists' statement takes on even greater force and urgency.

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4 O'Brien, et al., Molecular Epidemiology of Antibiotic Resistance in Salmonella From Animals and Human Beings in the United States, 307 New Eng. J. Med. 1 (July 1, 1982).

Conclusion

Clearly, the practice of feeding penicillin and tetracyclines to animals has created serious food safety risks. As the nature of these risks becomes more widely known, consumers inevitably will begin to question whether the meat they buy at the grocery store is safe to eat. To protect consumers' confidence in meat and to avoid further outbreaks of antibiotic-resistant diseases, prudent preventative measures should be taken immediately.

The Food and Drug Administration is now considering whether to impose an immediate ban on the use of penicillin and tetracyclines in animal feed pursuant to emergency provisions of the Food, Drug, and Cosmetics Act. Should FDA fail to take prompt, positive action, the Congress should itself impose the ban.